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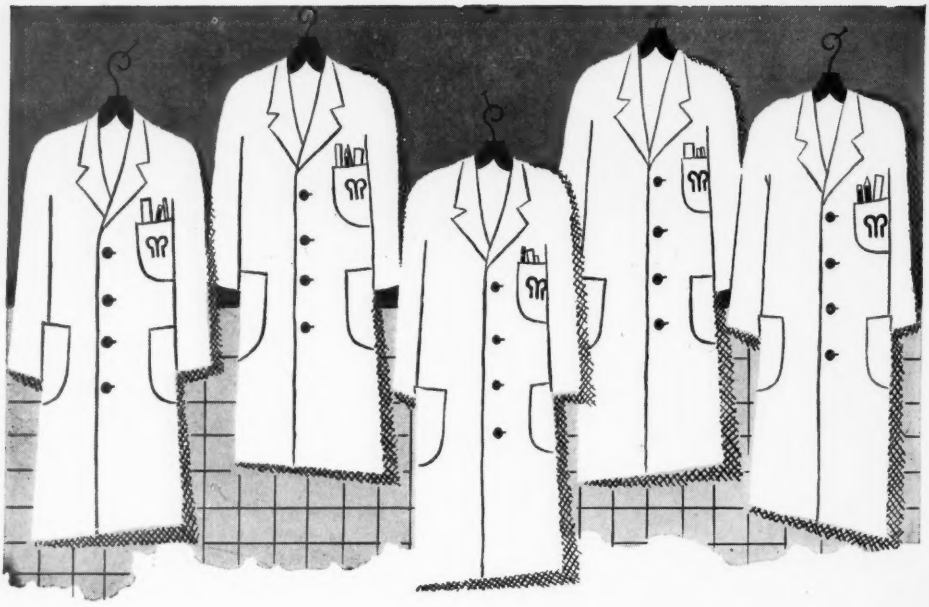

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ORAL STEROID MEDICATION IN RHEUMATOID ARTHRITIS*

HARRY FREEMAN, M.D., GREGORY PINCUS, Sc.D., SAMUEL BACHRACH, M.D., CARROLL W. JOHNSON, M.D., GEORGE E. McCABE, M.D. AND HAROLD H. MacGILPIN, JR., M.D.

From the Worcester Foundation for Experimental Biology, Shrewsbury, Mass., and the Arthritis Clinic of the Memorial Hospital, Worcester, Mass.

THE therapeutic efficacy of pregnenolone in rheumatoid arthritis has already been described in several publications and has been well summarized in a recent article by Henderson, Weinberg and Wright (1). Of the various reports, only one has been completely unfavorable—that of Guest, Kammerer, Cecil and Berson (2). In all these studies pregnenolone was administered by intramuscular injection and was beneficially effective in about half of the patients. A similar result was noted by us (3) in a previous experience with 30 patients treated solely by oral medication, of whom 15 showed major improvement, 11 minor improvement and 4 no improvement.

Our results with oral medication encouraged us to continue the study, so that the present paper deals with a total of 64 cases.

CLINICAL MATERIAL AND METHODS

The patients showed definite evidence of rheumatoid arthritis according to the standards of the New York Rheumatism Association as presented in the article by Steinbrocker, Traeger and Batterman (4). In the evaluation of the data, the patients were classified according to the degree of pro-

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gression of the disease (stages I to IV, ranging from slight osteoporosis to bone destruction and ankylosis), by the amount of limitation of functional activity (classes I to IV, ranging from no limitation to total incapacity), and finally by the response to therapy (grades I to IV, ranging from remission to unimprovement).

There were 17 men and 47 women included in the series. Their average age was 47.5 years and the average duration of the disease was 9.7 years. Of the entire group, 45 had a moderate to severe degree of arthritis by x-ray examination (stages III and IV, Steinbrocker's criteria) and 33 had moderate to severe impairment of functional capacity (classes III and IV, Steinbrocker's criteria). Thus the patients as a whole were middle-aged, were in a chronic stage of the disease and experienced marked anatomic and functional limitations as a result of their condition. There were no acute cases.

The patients on their initial visit had a complete physical examination and roentgenograms were made of the affected joints. Blood morphologic studies were made, including the circulating eosinophil counts together with sedimentation rates. These were later repeated at irregular intervals during the weekly visits of the patients.

As a routine procedure in most cases placebo medication was started for the first two weeks while the laboratory examinations were being completed. Only 3 patients reported improvement to a mild degree during this interval of time and are not included in this series. With the completion of the placebo period, the patients were given pregnenolone or pregnenolone acetate by mouth. No difference in results was found initially between the two drugs so that they were later used interchangeably. The initial dose was for the most part 500 mg. daily, smaller doses having been found to be less satisfactory. When improvement occurred it was evident usually by the end of two weeks and increased as the medication was maintained. In some cases in which the improvement was not striking, the dose was increased up to 700 or 800 mg. daily, but usually without any noticeable change.

RESULTS

The results achieved are shown in Table 1. Twenty-four patients (8 males and 16 females) showed a degree of improvement regarded as major (grade II), as evidenced by diminution of pain, increase in joint mobility, decrease in swellings and augmentation of strength. These patients represent 38 per cent of the total number studied, a reduction from the 50 per cent major improvement reported in our preliminary series of 30 cases. The average age of this group was 44.1 years and the average duration of the disease was 10.4 years. Seventeen of the 24 showed moderate to severe changes in the bone structure by x-ray examination and 11 of the 24 were

moderately to totally incapacitated by the disease. They were treated with pregnenolone for three to thirty weeks with an average period of 12.3 weeks. The period of treatment with pregnenolone was in most instances not continuous, as there was usually an interval in which the medication was discontinued in order to determine whether a relapse would occur.

The sedimentation rates were characteristically high in the majority of cases. In half, they came down to normal values; in the others there was usually a decrease in the rate of sedimentation but it did not reach normal limits. The mean sedimentation rate after treatment was 64 per cent of the original value.

TABLE 1. CLASSIFICATION OF 64 PATIENTS WITH RHEUMATOID ARTHRITIS ON THE BASIS OF GRADE OF IMPROVEMENT FOLLOWING THE ADMINISTRATION OF PREGNENOLONE

Grade of improvement	No. of patients		Per cent of total patients studied	Age of patient (yrs.)		Duration of disease (yrs.)		Duration of treatment (wks.)	
	M	F		Mean	Range	Mean	Range	Mean	Range
Major	8	16	38	44.1	31–71	10.4	0.5–20	12.3	3–30
Minor	5	21	41	51.0	24–74	9.6	1.0–25	5.7	2–19
None	4	10	21	43.7	35–65	9.5	0.5–23	4.3	2–7
Total	*17*	*47*							
Mean				*47.5*		*9.7*			

The circulating eosinophils varied widely in values from 50 to 881 per cu. mm. The mean value was 303. In two thirds of the cases there was a decrease in level, the average figure after medication being 216, a decrease of 28 per cent.

Twenty-six patients (5 men and 21 women) achieved a level of improvement of a less striking nature, but similar in characteristics. These represent 41 per cent of the cases. The average age of these patients was slightly higher, the mean being 51.0 years. The average duration of the disease was approximately the same as that of the previous group, 9.6 years. Fifteen of the 26 patients showed moderate to severe progression of the disease (stages III and IV) and 11 were moderately to totally incapacitated (classes III and IV). The average duration of treatment was 5.7 weeks, ranging from two to nineteen weeks. Again, in some instances, the treatment period was interrupted by intervals in which the medication was discontinued. The lesser response in this group is not in our opinion due to the shorter treatment period. The patients simply did not respond in two to three weeks

to as great a degree as those in the previous group and for this reason the medication was not maintained for as long a time.

The changes in the sedimentation rates were less striking. Only in one third of the cases with previously abnormal rates was there a reduction to normal. The average value after treatment was 74 per cent of the pretreatment level.

The circulating eosinophils were at a somewhat lower level than in the previous group. The average value was 179 per cu. mm. (range 39 to 274) as compared with 303 per cu. mm. in the more responsive group. The post-

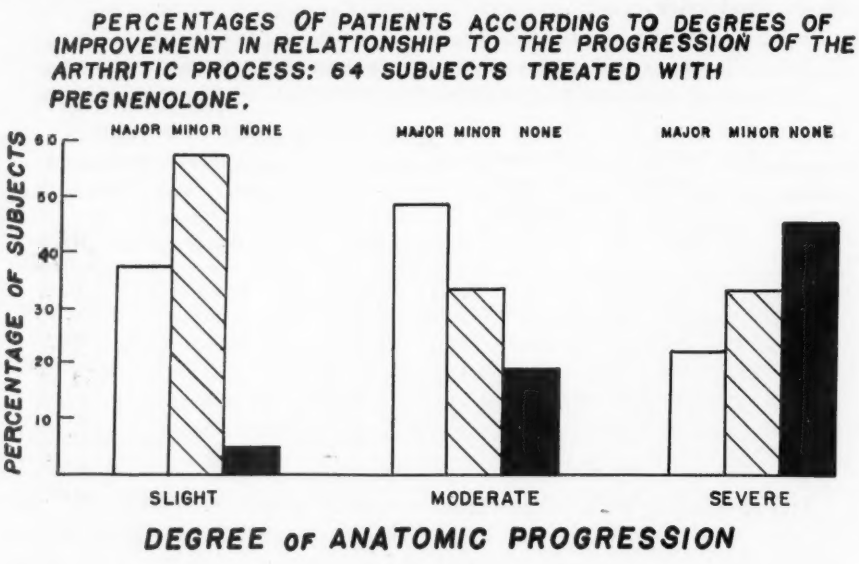

FIGURE 1

treatment level was essentially unchanged. The mean value was 184 per cu. mm.

The final group did not show any degree of improvement. They included 14 patients, 4 men and 10 women, constituting 21 per cent of the total number studied. The average age was 43.7 years, and the average duration of the disease 9.5 years. The treatment period was even shorter in this group, the mean being 4.3 weeks (range 2 to 7), simply because no response was evident.

In this group there was even less change in the sedimentation rates, only 15 per cent of the subjects showing a decrease to a normal value. The average post-treatment level was 94 per cent of the original value, an insignificant change.

In order to determine to what factors may be attributed the varying response of arthritic patients to pregnenolone, we have analyzed the data for the relationship of the degree of improvement to the anatomic progression of the disease, to the functional incapacity, to the chronologic age of the patients and to the duration of the disease.

Figure 1 shows the percentage of subjects in each of the three categories of improvement, grouped according to the progression of disease. The blank columns include those cases in which the improvement has been of

PERCENTAGES OF PATIENTS ACCORDING TO DEGREES OF IMPROVEMENT IN RELATIONSHIP TO THE AMOUNT OF FUNCTIONAL DISABILITY: 64 SUBJECTS TREATED WITH PREGNENOLONE.

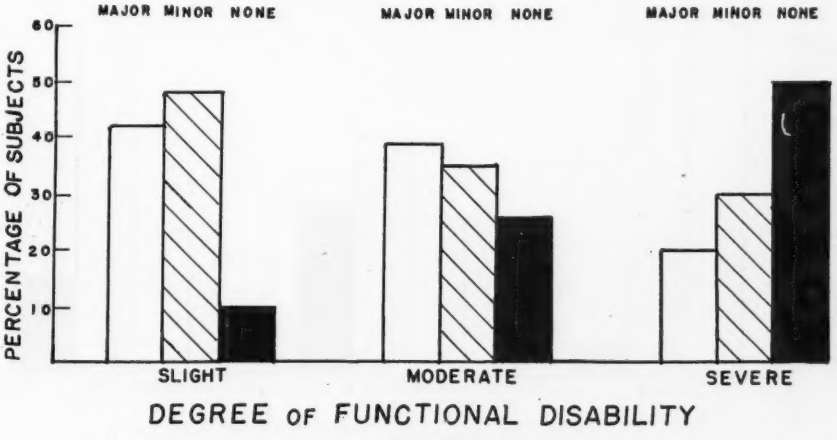

FIGURE 2

major extent; the stippled columns, those in which it has been of a minor degree; the solid columns, those in which there has been no change.

It is evident that of the patients with mild anatomic changes, 37 per cent showed striking improvement, 58 per cent showed minor improvement and only 5 per cent showed no improvement. Of the patients with moderate pathologic changes, 48 per cent showed major improvement, 33 per cent showed minor improvement and 19 per cent did not respond. In the severe cases, 22 per cent showed a major degree of improvement, 33 per cent a minor degree, and 45 per cent no change. Thus, there seems to be some gradation of the therapeutic response depending upon the severity of

the process, the worst cases showing the highest percentage of unimprovement.

A similar result is shown in the analysis of the relationship of the response to pregnenolone to the degree of functional incapacity exhibited before treatment (Fig. 2). Of those patients with little limitation, 42 per cent showed marked improvement, 48 per cent showed a lesser degree of improvement and only 10 per cent no improvement. In those with moderate disability, the corresponding values were 39, 35, and 26 per cent,

PERCENTAGES OF PATIENTS ACCORDING TO DEGREES OF IMPROVEMENT IN RELATIONSHIP TO AGE: 64 PATIENTS TREATED WITH PREGNENOLONE.

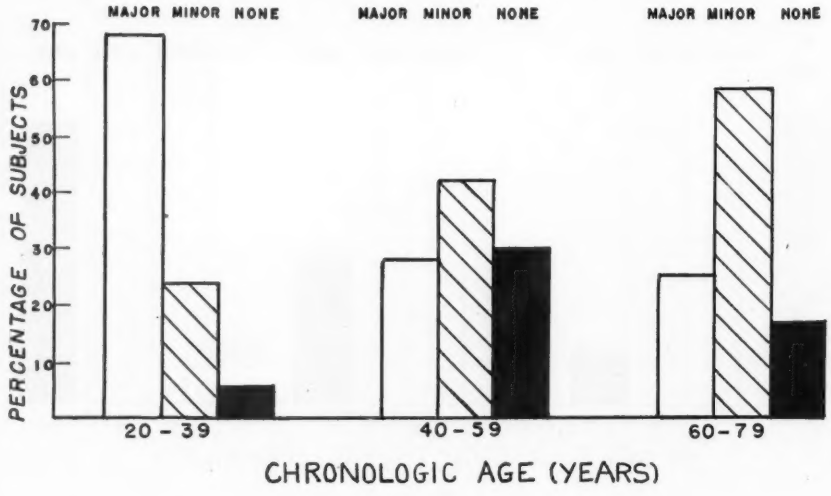

FIGURE 3

respectively. In those totally disabled, 20 per cent showed major improvement, 30 per cent minor improvement and 50 per cent no change. Again, the chances of a favorable response vary inversely with the degree of incapacity.

The relationship of the age of the patients to the degree of improvement is not so clear. As Figure 3 shows, in the youngest group, 68 per cent of subjects responded strikingly and another 25 per cent to a lesser degree. In the older groups, there were more minor than major improvements with a somewhat greater proportion of non-responders than in the first group.

The duration of the disease bore no relationship to the amount of improvement, the scatter of values being entirely at random.

A question of major interest is the duration of the ameliorative effect when pregnenolone was withdrawn. Data on this point were obtained in 18 cases in which major improvement occurred. In 11 of the patients, placebo tablets of identical appearance were substituted. In the other 7, no medication was given. All these patients showed a recurrence of symptoms at varying lengths of time, after which pregnenolone was administered again

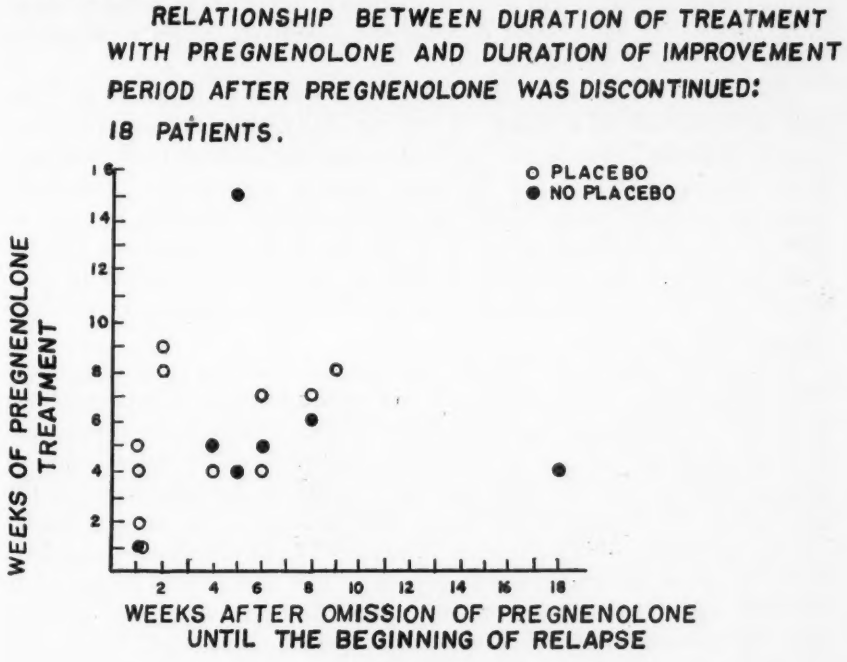

FIGURE 4

with a resumption of improvement to the same degree. Since the dosage of pregnenolone was essentially the same in all the patients, an analysis of the data was made to determine whether the length of treatment bore any relationship to the time at which relapses occurred. In the scatter diagram in Figure 4, each circle represents a patient. The empty circles are those patients to whom placebos were given when pregnenolone was discontinued, whereas the solid circles represent those to whom no medication was given. The majority of the cases show a definite positive relationship between the duration of treatment with pregnenolone and the length of time during which this improvement was maintained without the drug. The relation-

ship seems almost 1:1, with some degree of scatter. The role of the psychologic effects of the placebo medication in maintaining the improvement does not seem to be very important, since 5 of the 7 patients who had no medication fall in line with the general trend and 2 others, one shown at the top of the figure and the other to the extreme right, showed opposing tendencies.

It would seem, then, that relapses are almost inevitable after pregnenolone is withdrawn and that the drug must be used intermittently. The optimal period of treatment is as yet unknown, but it would certainly seem to be longer than eight weeks in order to insure longer average periods of quiescence than we have observed.

The optimal dosage of pregnenolone is still a moot point. Of 10 patients who were started on a dosage of 300 mg. daily, only 2 showed a satisfactory response in two weeks. In 1 other, 400 mg. daily did not show any improvement in this period. All other patients were started, therefore, on an initial daily dosage of 500 mg., which was increased in 18 cases to 600 mg.; in 4, to 700 mg; and in 1, to 800 mg. It is our impression that increasing the dose above 600 mg. brought no further improvement. In most of the cases the maximum improvement achieved was obtained on a daily dosage of 500 mg. daily.

In order to determine what the maintenance dose might be, 9 patients were selected who had previously shown a good response to pregnenolone, but in whom the disease had relapsed on discontinuance of the medication and had regained the previous level of improvement on reinstitution of therapy. In view of the fact that with complete discontinuance of the medication the disease on the whole does not relapse for several weeks, the clarification of this point was not expected to be simple. Nevertheless, some pertinent information was obtained. The dosage was decreased to 200–300 mg. daily until the previous point of improvement was reached, and was increased only when symptoms and signs recurred. This aspect of the study lasted for an average of thirteen weeks, ranging from ten to fifteen weeks. It was found that a satisfactory maintenance dosage in 1 patient was 300 mg.; in 5 patients, 400 mg.; in 2 patients, 500 mg.; and in 1 other patient, 600 mg. It would seem that, on the whole, 400 mg. daily is the minimum average daily dose for maintenance of improvement.

No consistent untoward effects were noted. There were occasional complaints of polyuria, fullness of breasts, and eructation of gas but no symptoms were persistent or marked. No effect was noted on blood pressure. No glycosuria was evident and in 2 cases of diabetes mellitus in this series, the diabetic condition was unchanged.

DISCUSSION

The psychologic factors in improvement under any form of therapy are not to be dismissed lightly, especially in view of the dramatic efficacy of ACTH and cortisone in this chronic and disabling disease. We have done our best to evaluate this factor by giving patients placebos both before the institution of pregnenolone therapy and during the period when pregnenolone was withdrawn. In only 5 per cent of all our patients has there been any improvement, even to a mild degree, during placebo therapy given before true medication, due primarily to the long progression of the disease in most of the patients who had run through the usual gamut of treatment with discouraging results. In addition, the relationship of the duration of the period of improvement after pregnenolone is discontinued to the length of the period of treatment, both in patients who received placebos and in those who did not, makes it unlikely that suggestion played an important role in the patients who experienced a major degree of improvement. Spontaneous remission as a cause for the improvement likewise seems largely ruled out when dealing with a fairly large group of cases; and furthermore, in all improved patients who were given placebos, the disease eventually relapsed.

It should be emphasized that our investigation is concerned with oral pregnenolone given in high dosage. It is difficult to make comparison with studies involving injectable pregnenolone. By our standards the dosages administered parenterally by Guest *et al.* (2) are inadequate, although Cohen, Goldman, Dubles and McBride (5) and Kling (6) obtained some remissions with similar low dosages. Our objections to the use of injectable pregnenolone have in part been previously given (3). We should like to emphasize that pregnenolone is an extremely insoluble steroid; in animal experiments one of us (7) has recovered pregnenolone crystals from the muscles of rabbits as long as four weeks after the injection of aqueous suspensions in large amount. Sterile abscesses have been noted and clear evidence of inflammation and walling-off at the injection site. We therefore view with caution results obtained with injected pregnenolone unless clear evidence of absorption is available. Evidence for the absorption of oral pregnenolone has been presented on the basis of metabolism studies in animals and man (8).

Pregnenolone, then, can be regarded as an aid in the treatment of arthritis. It is relatively less expensive than ACTH and cortisone, has no profound toxic or physiologic effects and certainly by the oral route is much easier for the patient. Its value may lie chiefly in indicating that many substances yet to be investigated may offer better clues to the treatment of this disease.

SUMMARY

Sixty-four patients with rheumatoid arthritis were treated with pregnenolone by mouth in dosages averaging about 500 mg. daily, over varying periods of time ranging from two to thirty weeks. Twenty-four patients experienced striking improvement; 26 showed minor improvement; and 14 showed no improvement. The usual maintenance dose was 400 mg. daily. There was a great tendency to relapse after the medication was discontinued. There was a direct relationship between the length of time pregnenolone was administered and the length of time improvement was maintained after the medication was discontinued.

Acknowledgments

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GAMETOGENIC FAILURE WITH HIGH URINARY GONADOTROPIN (FSH)

E. PERRY McCULLAGH, M.D., WILLIAM T. SIRRIDGE, M.D.* AND HAMISH W. McINTOSH, M.D.†

From the Cleveland Clinic and the Frank E. Bunts Educational Institute, Cleveland, Ohio

THE existence of a second testicular substance with hormonal activity was suggested by Mottram and Cramer (1) in 1923 when it was shown that castration cells appeared in the pituitaries of adult male rats that had received roentgen ray treatment to the testes. The dosage was such that the Leydig cells were preserved and the secondary sexual organs, namely the seminal vesicles and the prostate which they support, were maintained but the germinal epithelium of the seminiferous tubules was destroyed. They concluded: "The observations show that the two component tissues of the testis, the spermatogenetic tissue and the interstitial tissue, have two distinct and independent effects on the organism, and that of these two effects that of the interstitial cells is the more profound one."

Evans (2) in 1929 showed by implantation experiments that there was more gonadotropic hormone in the pituitary glands of cryptorchid animals than in the pituitary glands of normal animals.

Martins and Rocha (3) in 1931 demonstrated that the parabiosis of an infantile rat with a castrate induced a precocious sexual maturity of the former in a few days after junction; and when the castrated partner was the male, testicular implants or injection of macerated testes prevented the precocious sexual maturity of the female. The testicular material was not sufficiently androgenic to correct the atrophy of the accessory genitalia. These workers further postulated that the hormone regulating the hypophysis was probably secreted by the germinal epithelium.

Witschi, Levine, and Hill (4) in 1932 found that when male rats sterilized by x-ray (2400 R in 3 treatments) were united in parabiosis with normal females, the females developed irregularities in their estrus cycles; prolonged and eventually permanent estrus periods resulted. Their conclusion was "that the lack of spermatogenetic activity alone is responsible for the increase in hypophyseal activity in the x-ray sterilized rat."

McCullagh and Walsh (5) confirmed this work. They obtained a water-

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* Present address: Kansas City, Kansas.

† Present address: Vancouver, B.C.

soluble nonandrogenic extract from a bull's testes which they called "inhibin." The work at that time appeared to indicate that this extract caused atrophy of the prostate and seminal vesicles in normal rats. Vidgoff, Hill, Vehrs, and Kubin (6) in 1939 confirmed their observations, using similar preparations.

Nelson (7) in 1934, showed that in rats made cryptorchid by operation, changes occurred in the hypophysis in 75 days, in the seminal vesicles in 240 days and in the prostate in 400 days. The changes seen suggested a hormone level barely below that necessary for maintenance. It is known that in experimental cryptorchidism the germinal epithelium undergoes degenerative change before the interstitial cells. This then might suggest that the changes observed in the pituitary with formation of so-called castration cells can be correlated with the degeneration of the germinal epithelium, whereas the changes in the accessory sex organs are linked with the interstitial cells.

That testosterone in doses higher than necessary for prostatic maintenance is unable to inhibit the pituitary weight increase following castration can be easily demonstrated in experimental animals.

Table 1 gives comparative data of the body weights and weights of the pituitaries, prostates, and seminal vesicles of three groups of male rats—a control group, a group of castrate rats, and a group of castrate rats treated with 100 micrograms of testosterone propionate daily for twenty-one days. Pituitary weights show increases after castration, and in the testosterone-treated rats the 100 microgram daily dose of testosterone propionate did not inhibit such increases despite the fact that the dosage was more than enough to maintain prostatic and seminal vesicle size.

In this report it will be shown that in man excess gonadotropin can appear in the urine associated with germinal epithelial failure, while Leydig and Sertoli cells remain normal both histologically and functionally, as far as can be determined. However, it is recognized that some patients show considerable tubular abnormality without elevation of the urinary gonadotropin. These patients are not considered here.

CLINICAL ASPECTS

The 15 patients presented in this study showed no clinical evidence of androgen deficiency. One patient (Case 12) had gynecomastia. Body hair was normal in amount and distribution in all cases. Libido and potency were normal in all. The prostates were normal in size, shape and consistency in all. Male aggressiveness and demeanor were normal in all patients with the possible exception of Case 12. Any patients showing a suggestion of eunuchoidism clinically were excluded. The ages ranged from 19 to 41 years. Wassermann and Kahn tests, semen examinations and assays for

urinary gonadotropin were made in all; in all but one, urinary 17-ketosteroids were determined; and in all except the cryptorchid patients, testicular tissue was removed for biopsy. All patients were in good health except one (Case 14) who had had chronic nonspecific ulcerative colitis for three

TABLE 1

		Non-castrated controls	Castrated controls	Castrates—treated with testosterone
Body wt. (Gm.)	1)	255	290	318
	2)	258	280	277
	3)	260	287	292
	4)	262	255	305
	5)	255	278	294
	6)	257	272	287
Pituitary wt. (mg.)	1)	6.4	12.0	11.2
	2)	6.4	11.6	11.4
	3)	5.8	10.8	8.2
	4)	6.8	12.0	9.2
	5)	6.2	10.2	10.4
	6)	7.8	11.0	10.2
Prostate wt. (mg.)	1)	257.0	Atrophied	433.8
	2)	289.2	Atrophied	351.9
	3)	164.8	Atrophied	496.6
	4)	282.2	Atrophied	321.9
	5)	252.0	Atrophied	361.2
	6)	311.6	Atrophied	310.0
Seminal vesicle wt. (mg.)	1)	461.2	78.2	652.4
	2)	482.8	100.0	509.2
	3)	242.4	90.0	511.6
	4)	338.6	100.2	515.6
	5)	392.0	134.6	486.6
	6)	410.0	102.0	490.0

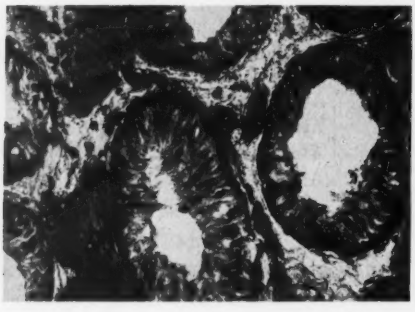
years. This patient had been treated with large doses of various sulfonamide drugs and at the time of this study was in a good nutritional state, having only one to two stools daily. Patients 1 and 2 were cryptorchid. Patient 15 had had a traumatic injury to the left testis and also had had a Neisserian infection with possible testicular involvement.

The important points in the histories, physical examinations, and testicular biopsies of the patients are as follows:

Case 1. A man aged 41 years had been married for three years but had no children. His height was 72 inches and his weight 191 pounds. He had a history of mumps in childhood and again at the age of 24, without evidence of orchitis. He was examined because of cryptorchidism and childlessness. Libido and potency were normal. His penis was normal in size and there was a normal amount and distribution of hair; the testes were present in the inguinal canals; and the prostate was of normal size, shape, and consistency. Testicular biopsy was impossible because of bilateral cryptorchidism.

Case 2. A married man of 36 years had no children. His height was 70 inches and his weight 160 pounds. He had a history of mumps at the age of 5 years. Examination was made because of bilateral cryptorchidism, with interest in establishing fertility. Libido and potency were normal. The penis was normal in size; there was a normal amount and distribution of body hair with a heavy beard; the testes were visible and palpable at the lower ends of the inguinal canals but could not be brought into the small scrotum; and the prostate was of normal size, shape and consistency. There was no testicular biopsy because of cryptorchidism.

Case 3. A single man aged 29 years was 65 inches in height and weighed 128 pounds. There was no history of mumps, orchitis, or known infection, but there was a history of handling radium once monthly for the year preceding examination. Examination was made because of suspected infertility. Libido and potency were normal. The penis was normal in size; there was a normal amount and distribution of hair; the testes and prostate were normal in size and consistency. *Testicular biopsy:* absence of spermatogenic elements; moderate hyperplasia of the interstitial cells; cells of the Sertoli type normal in number and appearance; slight basement membrane thickening (Fig. 1).



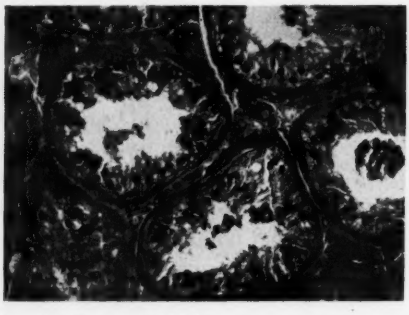
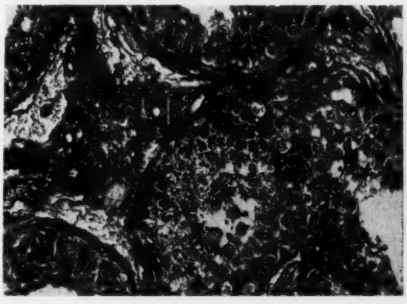


FIG. 1. Testicular structure in Case 3. ×225.

FIG. 2. Testicular structure in Case 4. ×225.

Case 4. A man aged 34 years had been married for six years but had no children. His height was 69 inches and his weight 178 pounds. There was a history of mumps without orchitis and of 6 x-ray treatments to the thighs using a metal guard to the scrotum. Libido and potency were normal. There was a slight decrease in penile size; the testes were small and soft; but the prostate was of normal size and consistency. *Testicular biopsy:* tubules small and irregular in shape; complete absence of spermatogenic elements; moderate interstitial cell hyperplasia, possibly due to abnormal relationship of small tubules and normal Leydig cells; cells of Sertoli type normal in number and appearance; slight to moderate thickening of the basement membrane (Fig. 2).

Case 5. A man aged 32 years had been married for eleven years but had no children. His height was 77 inches and his weight 188 pounds. There was a history of mumps in childhood without known orchitis. Examination was made because of childlessness. Libido and potency were normal. The penis was normal in size; there was a normal amount and distribution of body hair; the testes and prostate were normal in size, shape, and consistency. *Testicular biopsy:* moderate hypoplasia of spermatogenic elements; slight hyperplasia of interstitial cells; cells of Sertoli type normal in number and appearance; slight to moderate basement membrane thickening in scattered tubules. Where the germinal epithelium was relatively spared, the cells had lost their orderly arrangement and appeared disarranged as though they had been stirred. It is possible, however, that this was an artefact (Fig. 3).



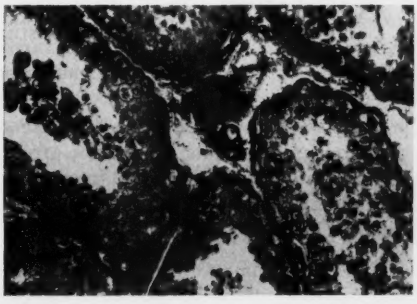


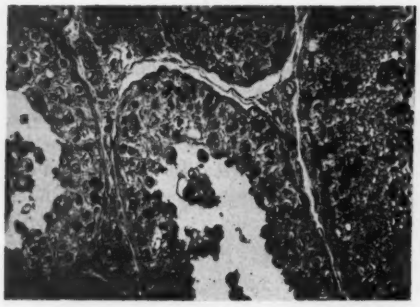
FIG. 3. Testicular structure n Case 5. ×225.

FIG. 4. Testicular structure in Case 6. ×225.

Case 6. A man aged 27 years had been married for four years but had no children, although contraceptives were not used. His height was 77 inches and his weight 220 pounds. There was no history of venereal disease or mumps. Genital development was normal; the testes were normal in size and consistency, and the prostate was normal. Secondary sexual characteristics were normal. *Testicular biopsy:* varying degrees of thickening of the basement membrane in many tubules; all spermatocytic elements reduced in number (Fig. 4).

Case 7. A man aged 31 years had been married for three years, without children. His height was $67\frac{3}{4}$ inches and his weight 156 pounds. There was a history of mild mumps without orchitis and of primary tuberculosis, minimal and inactive. Examination was made because of infertility. Libido and potency were adequate; and secondary sex characteristics were normal. *Testicular biopsy:* moderate hypoplasia of spermatogenic elements; maturation arrest chiefly at the level of the primary spermatocyte; a questionable rare spermatid; appearance suggestive of interstitial cell hyperplasia; cells of Sertoli type normal in number and appearance; slight irregular thickening of the basement membranes in rare tubules (Fig. 5).

Case 8. A man aged 31 years had been married for five years, without children. His height was 73 inches and his weight 212 pounds. There was no history of mumps or venereal disease. Examination was made because of childlessness. Libido and potency were normal. The penis was normal in size; there was normal hair growth and distribution; the testes were slightly smaller than normal but of normal consistency; and the



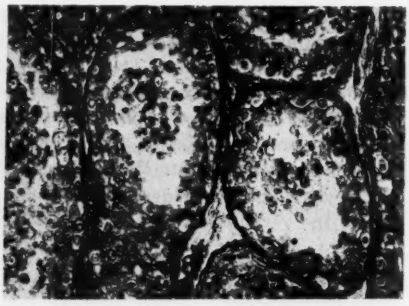
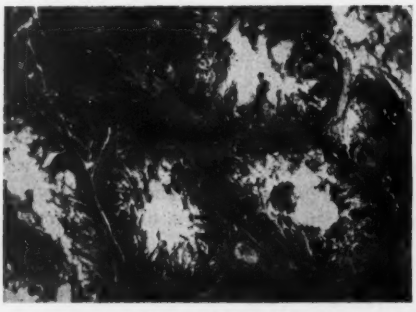


FIG. 5. Testicular structure in Case 7. ×225.

FIG. 6. Testicular structure in Case 8. ×225.

prostate was of normal size and consistency. *Testicular biopsy:* moderate reduction in spermatogenic elements; maturation arrest chiefly at the secondary spermatocyte stage; many abortive mitoses; normal interstitial cells; cells of Sertoli type normal in number and appearance; slight to moderate thickening of the basement membranes of some tubules (Fig. 6).

Case 9. A man aged 30 years had been married for seven years but had no children. His height was 69 inches and his weight 187 pounds. There was a history of mumps at the age of 16, without known orchitis. Examination was made because of childlessness. Libido and potency were normal. The penis was normal in size; the testes and prostate were of normal size and consistency; and there was normal male hair growth and distribution. *Testicular biopsy:* aplasia of spermatogenic elements; Leydig cells normal in number and appearance; tubules well lined with cells of Sertoli type which were normal in number and appearance; slight to moderate thickening of the basement membranes, with a tendency to wrinkling (Fig. 7).



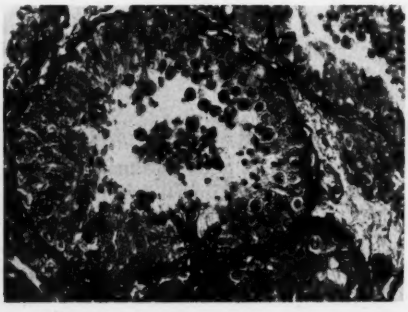


FIG. 7. Testicular structure in Case 9. ×225.

FIG. 8. Testicular structure in Case 10. ×225.

Case 10. A man aged 24 years had been married for three years but had no children. His height was 72 inches and his weight 164 pounds. There was a history of mumps at the age of 10, without known orchitis. Examination was made because of childlessness.

Libido and potency were good. The penis was normal in size; there was normal hair growth and distribution; the testes were firm but smaller than normal, the left being smaller than the right; and the prostate was larger than normal but firm and nontender. *Testicular biopsy:* moderate reduction in spermatogenic elements; many deformities of the nuclei in cells in each stage of spermatogenesis; great reduction in the relative number of secondary spermatocytes and spermatids; slight interstitial cell hyperplasia; cells of Sertoli type normal in number and appearance; considerable thickening of some basement membranes of the tubules of the right testis (Fig. 8).

Case 11. A man aged 22 years had been married for two years but had no children. His height was 70 inches and his weight 144 pounds. He had a history of mumps without known orchitis. Examination was made because of childlessness. Libido and potency were normal. The penis was normal in size; there was normal hair growth and distribution; and the testes were of normal size, shape, and consistency. *Testicular biopsy:* tubules of uniform size and contour; no fibrosis; exceptionally large spermatogonia, few of normal size; few primary spermatocytes; some of these cells extremely large with two degenerating nuclei; no spermatogenesis beyond the primary spermatocyte (Fig. 9).

Case 12. A man aged 41 years had been married for eighteen years but had no children. There was no history of mumps. Examination was made because of childlessness. Libido and potency were normal. The penis was normal in size; there was a normal amount and distribution of body hair; and the testes were of normal size, shape, and consistency. *Testicular biopsy:* moderate hypoplasia of spermatogenic elements, which had lost the normal orderly arrangement and showed little suggestion of layers; slight hyperplasia of the interstitial cells; cells of Sertoli type normal in number and appearance; moderate basement membrane thickening in some tubules especially in the left testis.

Case 13. This single man was 21 years old. His height was 70 inches and his weight 207 pounds. He had been overweight since early adolescence. His secondary sexual characteristics were normal; the prostate was normal in size; but both testes were small and soft, about half the normal size. Gynecomastia was present. The semen contained many abnormal spermatozoa. *Testicular biopsy:* (right testis) pronounced hypoplasia of spermatogenic cells; an occasional spermatogonium, but nothing more mature; tubules of normal size, well-lined, and with normal appearing Sertoli cells; Leydig cells abundant and apparently normal (Fig. 10).

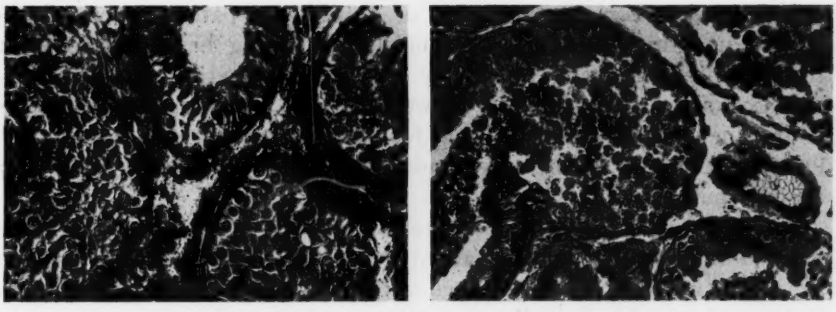


FIG. 9. Testicular structure in Case 11. ×225.

FIG. 10. Testicular structure in Case 13. ×225.

Case 14. A man aged 30 years had been married for four and one half years but had no children. His height was 71½ inches and his weight 153 pounds. He had had mumps without orchitis, and also had a history of chronic ulcerative colitis for three years. Examination was made because of childlessness. Libido and potency were normal. The penis was normal in size and the testes were of normal size and consistency. *Testicular biopsy:* active spermatocytogenesis but little spermatogenesis; interstitial cells, cells of Sertoli type, and basement membranes normal (Fig. 11).

Case 15. A man aged 30 years had been married for five years but had no children. His height was 69½ inches and his weight 172 pounds. There was no history of mumps or orchitis but he had sustained an injury to the left testis at the age of 18, and there was a history of Neisserian infection. Examination was made because of childlessness. Libido and potency were adequate. The penis was normal in size; the left testis was small and soft but the right testis was of normal size and consistency; and the prostate was at the lower limit of normal in size. *Testicular biopsy:* hypoplasia of spermatogenic elements; slight spermatogenesis; slight sclerosis of tubules; moderate relative interstitial cell hyperplasia; cells of Sertoli type normal in number and appearance (Fig. 12).

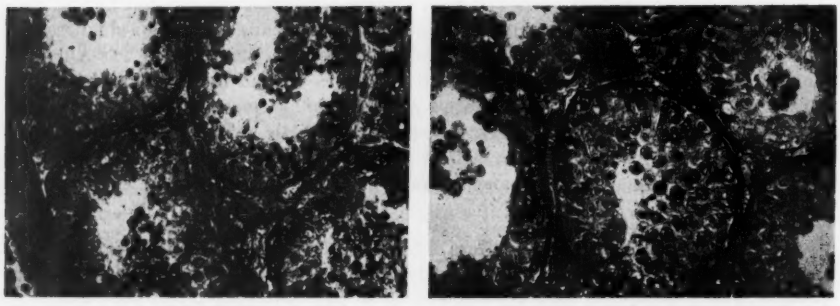


FIG. 11. Testicular structure in Case 14. ×225.

FIG. 12. Testicular structure in Case 15. ×225.

SPECIAL LABORATORY STUDIES

Urinary gonadotropin: As shown in Table 2, all patients excreted excessive amounts of the pituitary follicle-stimulating hormone (FSH) in the urine. The normal excretion by the assay method used (Klinefelter, Albright, and Griswold (8)) is between 13 and 105 mouse units per 24-hour urine volume. The usual range for adult males is from 26 to 52 mouse units. All the patients presented had gonadotropin excretion levels higher than normal.

17-Ketosteroids: Urinary 17-ketosteroids (17-KS) were determined by the method of Bowman (9) in all patients except in Case 13. In each instance they were within the normal range of 6 to 14 mg. per twenty-four hours. Only rarely are levels higher than 14 mg. and less than 6 mg. found in normal adult males.

TABLE 2

Case No.	Urinary gonadotropin, m.u./24 hrs.	Urinary 17-ketosteroids, mg./24 hrs.	Sperm count (millions)		Semen vol., cc.
			Per cc.	Total	
		Cryptorchidism			
1	105–212	12.6	0		2.0
2	318–424	6.9	0		3.6
		Irradiation injury			
3	105–212	11.2	0		5.2
	105–212		0		4.0
	105–212				
	105–212				
4	105–212	13.2	0		1.4
		Tubular fibrosis			
5	318–424	7.5	0		7.2
6	212–318	7.4	10.0	73.0	7.3
		Maturation arrest			
7	212–318	10.0	0		6.7
	105–212	(androgens, I.U. ± 8/dy.)*	0		11.2
8	212–318	11.0	0		1.9
			0		2.2
		Germinal aplasia			
9	212–318	8.3	0		7.5
		Abnormal spermatogenesis, spermatocytic disorganization, cause unknown			
10	52–105	7.2	0		2.6
	105–212		0		4.6
	105–212				
11	105–212	8.8	0		
			0		
12	212–318	9.7	0		2.9
			0		
			0		
13	105–212		1.0	3.5	3.5
		Possible toxic or infectious injury			
14	105–212	9.7	11.0	76.0	6.6
			13.0	70.0	5.4
			4.0	20.0	5.2
15	212–318	11.9	3.6	11.1	3.1

* Done on 3-day urine specimens after acid hydrolysis—Gallagher-Koch capon comb growth method.

Semen volume: In Case 13 the patient had no evidence of androgen deficiency clinically and had normal development of all secondary sex characteristics. He had normal androgen production as judged by his semen volume.

If androgen production is normal for a sufficient time, the genital growth and secondary sexual characteristics are normal. These characteristics, however, remain relatively unchanged after gonadal failure occurs in adult life and therefore changes are not of much value in judging the circulating androgens. If androgens are withdrawn from the body, the prostate and seminal vesicles atrophy rapidly and their secretions diminish noticeably. The semen volume depends largely upon the secretion of the prostate and seminal vesicles; thus the volume of the semen is a good index of the androgen production of the testes, and its measurement affords a method of assay of androgenic activity. In the patients presented here the semen volume was normal in all, with the possible exception of Patient 4.

Semen examination: The results of the semen examinations were as listed in Table 2. Eleven patients were azoospermic, and 4 patients had severe oligospermia with a higher number of abnormal forms present than seen in normal semen. The values of normal semen examination in men under 40 years of age are considered to be 50–100 million spermatozoa per cubic centimeter and over 200 million spermatozoa per total specimen.

Testicular biopsy: Reports of the testicular biopsies are included with the clinical histories of all the patients except in Cases 1 and 2. In these 2 patients, cryptorchidism rendered biopsy impossible. In all cases the interstitial cells and the cells of Sertoli appeared normal. The germinal epithelium was abnormal in all patients, varying from a histologic appearance which was relatively near normal to a complete absence of germinal cells as in the sections from Patient 3.

A few patients were treated, and brief notes regarding response to therapy are shown in Table 3. Patients not included were not treated.

DISCUSSION

Nearly all the evidence in favor of a second testicular hormone and a possible explanation of the excess urinary gonadotropin had been experimental until 1942, when Klinefelter, Reifenstein, and Albright (10) published a study of 9 patients with high FSH, aspermatogenesis without aleydigism, and gynecomastia. Examination of the histories, physical findings, and laboratory studies leads us to suspect that 4 of these patients had hypoleydigism. The testicular biopsy specimens showed the absence of the normal constituents of the seminiferous tubules. In 1947 del Castillo, Trabucco, and de la Balze (11) presented data on 5 patients, which sug-

TABLE 3

Case No.		Sperm count (millions)	
		Per cc.	Total
4	.....	0	
	Testosterone, 25 mg. 3×wk. for 4 wks. Urinary gonadotropin fell to normal	not repeated	
7	.....	0	
	Antuitrin S, 500 I.U. q. 2nd day for 3 wks.	0	
8	.....	0	
	Gonadotropin (Schering), 26 synergistic units daily for 28 doses		
	APL, 250 units in same synergist daily for 28 doses	0	
9	.....	0	
	Pit. Gonadotropin (Schering), 125 rat units/day for 3 wks.; omitted for 1 wk.; repeated for 3 wks.	0.4	
10	.....	0	
	Pit. Gonadotropin (Schering), 1 cc. daily for 3 wks.	9	38.7
	1 cc. daily for 4 wks.	0	
	Androstandiol, 15 mg. q. 2nd day for 3 wks.	0	
14	.....	11.0	76.0
	At time of assays and sperm counts had active *ulcerative colitis;* was taking *sulpha drugs* and *vitamins A & E*. Six months after marked improvement	13.0	70.0
	wife became pregnant	4.0	20.0
15	.....	3.6	11.0
	Gonadotropic Factor (Squibb), 25 units q. 2nd day for 4 wks.	0.6	1.6
	Pregnenolone, 10 mg. q. 2nd day for 4 wks.	0.2	0.4
	No therapy—2 mon.	1.0	2.8
	No therapy—5 mon.	0	0
	Pit. Gonadotropin (Schering), 1 cc. q. 2nd day for 17 doses	0	0

gested that the Sertoli cells are the source of a hormone similar to estrogen which regulates the follicle-stimulating hormone production of the pituitary. Although it cannot be assumed that relatively normal cellular appearance proves normal function, it is nevertheless true that the one portion of the tubules which is well maintained in the majority of our patients,

is the Sertoli element. It appears to us that our findings in this respect are at variance with those of del Castillo.

In the group of patients here presented urinary gonadotropin was elevated in all patients (Table 2), and the 17-ketosteroid excretion was within normal limits in all patients in whom determinations were made. No determination was made in Case 12, but here the semen volume was strictly normal so that circulating androgens were almost certainly normal.

It is generally conceded that testosterone is of little or no importance in the regulation of FSH production.

It has been demonstrated experimentally that the presence of normal interstitial and Sertoli cells does not prevent pituitary hypertrophy and the appearance of castration cells (1). It has further been demonstrated that in patients with typical clinical hypogonadism, substantiated by testicular biopsy and the determination of 17-ketosteroid excretion, large amounts of testosterone may not suppress gonadotropin excretion to the normal level (12). Androgen deficiency cannot be a factor in elevating the FSH in the patients presented in this paper. Further evidence of the lack of causal relationship between androgen deficiency and elevated urinary gonadotropin has been found in the study of 3 patients with unquestionable hypogonadism, who showed some spermatogenesis (to be reported elsewhere). Their testicular biopsy specimens showed an absence or near absence of Leydig cells without gross lesions in the seminiferous tubules; semen contained some spermatozoa, and repeated determinations did not show an excess of urinary gonadotropin.

The possibility of the urinary gonadotropin titer being high in testicular failure because of nonutilization of these substances by the gametogenic cells has been mentioned by Heller.

In the light of present evidence this explanation must be considered a distinct possibility. However, the evidence summarized in the beginning of this paper would suggest that the presence of a second testicular hormone must be considered also. To our minds the strongest single factor against the nonutilization theory of Heller is the demonstration of excess gonadotropin in the pituitary gland itself in cryptorchid animals (2). Another point which seems an important argument against the nonutilization theory relates to the effect of estrogens in testicular failure. Small doses of estrogens given to hypogonadal men will quickly reduce urinary gonadotropin titers to normal (12, 13). It is obvious that the utilization of gonadotropin is not a factor under these circumstances. This strongly suggests the possibility, that whether or not the nonutilization theory be subsequently proven correct, there must be other factors of importance.

It is to be emphasized that the patients presented here had normal Sertoli cells as well as normal Leydig cells. In contrast, however, the ger-

minal epithelium was distinctly abnormal, although it varied markedly. It was completely absent in 2 patients (Case 3—exposed to radium; and Case 4—treated by x-ray). In others, the cells maintained a relatively good histologic appearance, though physiologically abnormal as evidenced by azoospermia. Two patients (Cases 1 and 2) probably had absence of gametogenic elements also, although no biopsy specimens could be obtained due to cryptorchidism. Their semen volume was normal. It would appear highly probable that the germinal epithelium rather than the Sertoli cells is the chief testicular regulator of the follicle-stimulating activity of the pituitary gland. The excess of urinary gonadotropin in the patients presented is interpreted as the result of deficiency of a second testicular hormone, inhibin, secreted by the germinal epithelium.

Huggins (14) has shown that Sertoli cell tumors in dogs may produce estrogens. Because of our knowledge of the pituitary-inhibiting power of estrogens, obvious questions arise which cannot be answered satisfactorily in terms of application to human physiology. In considering the Sertoli cell as a possible pituitary regulator, Howard *et al.* (13) have presented arguments which have convinced them that the "x" hormone or "inhibin" arises from this source. However, their Cases 79, 80, 82, 83, 85, 88, 91, 92, 94, 95, and 96 have high titers of urinary gonadotropin and normal Sertoli cells.

SUMMARY

1. Fifteen patients with azoospermia and oligospermia are presented. Two were cryptorchid, 2 had irradiation injury to the testes and 11 had various types of impaired tubular function.

2. Assays of urinary gonadotropin showed high titers in all patients.

3. Assays of urinary 17-ketosteroids were normal in all cases.

4. Circulating androgens were judged to be normal because these patients had normal secondary sexual characteristics, normal prostatic size and normal semen volume.

5. Testicular biopsy specimens showed normal-appearing Leydig cells and Sertoli cells; basement membranes varying from the normal appearance to that of moderate thickening; and germinal epithelium varying from almost normal to complete absence.

6. It is suggested that the germinal epithelium is a likely source of a second testicular hormone ("inhibin") which regulates gonadotropin production by the pituitary gland.

Acknowledgment

We wish to thank Dr. Earl T. Engle for assistance in evaluating the testicular biopsy findings.

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EVALUATION OF AN ESTROGEN, ANDROGEN, ESTROGEN-ANDROGEN COMBINATION, AND A PLACEBO IN THE TREATMENT OF THE MENOPAUSE*

ROBERT B. GREENBLATT, M.D., WILLIAM E. BARFIELD, M.D., JOSEPH F. GARNER, M.D., GUY L. CALK, M.D. AND JOHN P. HARROD, JR., M.D.

From the Department of Endocrinology, Medical College of Georgia, Augusta, Ga.

CONTROVERSY has long existed over the efficacy of the large variety of therapeutic agents advocated for management of symptoms of the menopause. The role of estrogens in the management of the menopausal patient is well established. There are those, however, who feel that the need for this type of treatment has been overemphasized (1, 2). It has been claimed that "suggestion" plays an important role in therapy, and that placebos are equally as effective as estrogens (3, 4, 5, 6). The use of androgen therapy in lieu of estrogens has been suggested (7), and it has been claimed that combined estrogen-androgen therapy may be superior to estrogen therapy alone (7, 8, 9). Hence, there exists wide variations of opinion regarding treatment of menopausal symptoms.

In this report, our objectives are:

1. To establish the comparative effectiveness of a placebo, an estrogen, an androgen, and a combination of estrogen and androgen in the management of symptoms of the menopausal syndrome.

2. To compare the therapeutic effect of each of these agents in the individual patient.

3. To present some of the considerations necessary in evaluating a clinical study of this kind.

METHOD OF STUDY

Many difficulties were foreseen in attempting this study. Prerequisite for a useful clinical study was a method of obtaining data which could not possibly be influenced by pre-existing prejudice or preference on the part of the investigators. In order to eliminate personal equations in evaluation of a given substance, and in order to circumvent the factors of suggestion

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Miss M.B., w.f. 52. Menopause. Hot flashes and headaches. Smear 2 plus (slight estrogen deficiency).

AE	1	2	3	4	
Dec.	X				Complete relief of headaches and hot flashes. Smear 4 plus.
Jan.				X	Symptoms worse than before treatment. Smear 2–3 plus.
Feb.			X		Complete relief. Smear 3 plus.
Mar.		X			Complete relief. Increased libido, acne. Smear 3 plus.
Apr.	X				Complete relief. Smear 4 plus.

Patient obtained equally good results with AE-1, 2 or 3.

FIGURE 1

Miss R.N., w.f. 46. Surgical castration. Hot flashes—20 per day.

AE	1	2	3	4	
May	X				Complete relief. Smear 3 plus.
June		X			Complete relief. Smear 3–4 plus.
July					Hot flashes returned 1 wk. after stopping AE-2.
Aug.			X		75% relief, libido increased. Smear 2–3 plus.
Sept.			X		Same, occasional hot flash. Smear 3 plus.
Oct.				X	Hot flashes 20 per day, nervous. Smear 2 plus.
Nov.			X		Hot flashes stopped. Bled 2 days. Increased libido.
Dec.			X		Same. Slight hair growth. Bled 2 days.
Jan.		X			Complete relief.
Feb.	X				Complete relief, greater calm. Smear 3–4 plus.
Mar.		X			Best of all. Complete relief, increased well-being.

Patient stated preference for AE-2 because of improved well-being and libido in addition to control of hot flashes.

FIGURE 2

and psychotherapy in medication, the Eli Lilly Research Laboratories made available for this study four types of tablets—all similarly prepared in similar bottles labeled, "AE-1," "AE-2," "AE-3," and "AE-4." We did not know specifically the content of any of the AE preparations; however, we were informed that one contained an estrogen (diethylstilbestrol), one contained an androgen (methyltestosterone), another contained a combination of these, and the other was simply a placebo. Without knowledge of the actual type of medication being administered, an unbiased opinion could be rendered in evaluation of the response to medication (Fig. 1).

Mrs. J.S., w.f. 52. Menopause. Hot flashes and formication. (Hysterectomy.)

AE	1	2	3	4	
July	X				Complete relief. Slight increase in libido.
Aug.					Symptoms returned 3 wks. after stopping AE-1.
Sept.		X			90% relief. Increased libido, nervousness.
Oct.					
Nov.			X		Better than AE-2 or AE-1.
Dec.					Recurrence of symptoms.
Jan.				X	No relief. Smear 2–3 plus.
Feb.			X		80% relief. Occasional hot flashes. Smear 3 plus.
Mar.			X		Not as good as AE-1 now.
Apr.				X	No relief. Complete return of symptoms.

FIGURE 3

Patients with menopausal symptoms were given, as a rule, a bottle containing 100 of one or another of the tablets. The usual dosage was 1 tablet three times daily for thirty days. The interviews were brief and subjective symptoms were noted. The medication was changed at monthly intervals so that patients in this series were given from 2 to 10 courses of therapy in varying sequence (Fig. 2). In some instances sufficient time was allowed to elapse between courses of therapy to permit a return of symptoms (Fig. 3).

Objective factors were observed by studying the cytologic changes in vaginal spreads. Occurrence of bleeding, breast turgidity, pelvic congestion,

acne, and changes in libido were also noted, and patients were questioned at each monthly interview regarding changes in their initial subjective symptoms such as "hot flashes," insomnia, formication, and nervousness. It was recognized, of course, that all patients with symptoms usually referable to the menopause were not necessarily suffering from an hypoestrogenic state; however, since indication for therapy must often be based on

TABLE 1. *AE* PREPARATIONS IN THE TREATMENT OF THE MENOPAUSE (SELECTED CASES)

Patient	Age (yrs.)	Response to			
		AE-1	*AE-2*	*AE-3*	*AE-4*
1. D.E.S.	50	++++	++++	+++	+
2. R.N.(S)*	46	++++	++++	++++	0
3. H.G.O.(S)	44	++++	++++	0	0
4. J.C.(S)	37	++++	++++	++	0
5. E.E.H.(S)	35	++++	++++	++	0
6. W.E.M.(S)	23	++++	++++	+++	0
7. J.R.G.	48	++++	++++	++	0
8. K.E.F.(S)	25	++++	++++	+++	++
9. J.S.	48	++++	++++	++++	0
10. J.M.S.	62	++++	++++	++++	++
11. J.W.M.(S)	24	++++	++++	0	++
12. R.K.M.	45	++++	++++	++	—
13. O.R.P.	48	++++	++++	+++	0
14. M.C.H.	35	++++	++++	++	—
15. A.L.J.	53	++++	+++	++	0
16. W.H.J.	41	+++	++++	++	0
17. G.N.	45	++++	—	++++	+
18. M.B.	52	++++	++++	++++	0
19. H.W.	37	++++	++++	++++	—
20. V.G.P.	52	++++	—	—	++
21. J.B.P.	50	—	+++	+++	—
22. H.F.A.	47	+++	+++	++++	0
23. M.J.C.	52	++	++	+	0
24. W.S.E.	51	+++	++++	+	0
25. L.H.	46	++++	++	0	0
26. E.B.	48	++++	++++	+++	++
27. M.B.	44	+	+++	+	0
28. O.M.S.	45	++++	++++	+++	0
29. A.P.	38	−	+++	++	—
30. H.J.H.(S)	42	+	+	—	—
31. H.T.(S)	27	++++	—	+++	—

Response to therapy: ++++ = excellent; +++ = good; ++ = fair; 0–+ = poor.
*S = surgical menopause.

a wide variety of subjective symptoms, we felt that it would be unfair to establish rigid criteria for admission to the series. We considered also that true vasomotor symptoms of the menopause may often precede the development of hypoestrogenic changes in vaginal cytology (10, 11, 12). Observations were made on both private patients and patients referred to the Endocrinology Clinic of the University Hospital. Patients ranged in age from 23 to 62 years, the average being 44 years. Two hundred and eighty-four courses of therapy were administered to 102 patients. Results of therapy are recorded in Tables 1 and 2, and individual case studies are reported in Figures 1–5.

TABLE 2. ANALYSIS OF RESPONSE TO THERAPY WITH *AE* PREPARATIONS IN 74 PRIVATE PATIENTS AND 28 CLINIC PATIENTS WITH 284 COURSES OF THERAPY

Therapy	Courses of therapy		Percentage of patients				
	Private	Clinic	With nausea	With increased libido	With acne, hoarseness, or hirsutism	With intact uterus and bleeding following treatment	With no improvement
AE-1 Diethylstilbestrol, 0.25 mg.	67	21	30.5	12.3	0	34.2	3.1
AE-2 Diethylstilbestrol, 0.25 mg. Methyltestosterone, 5.0 mg.	54	19	4.0	23.5	13.2	30.5	10.4
AE-3 Methyltestosterone, 5.0 mg.	44	19	5.2	42.0	12.8	0.98	23.6
AE-4 Placebo	36	24	3.6	1.8	0	0	83.8

RESULTS

An initial evaluation of our records at the conclusion of this study revealed some perplexing factors. In some cases, more noticeable among the clinic patients, all the tablets appeared to give some degree of subjective improvement of symptoms, regardless of the sequence of administration. Many of these patients were psychoneurotics who were in the habit of visiting many of the other clinics and were receiving a variety of medicaments including sedatives. The clinic patients who were not receiving additional therapy and who were actually true menopausal patients fell into essentially the same pattern of response as our private group of cases who were more intelligent, reliable and under better control conditions. Many patients did not continue to return regularly for the five or six months necessary to obtain comparative results of all four types of therapy. We felt that some were warranted in their failure of cooperation because many,

upon receiving the placebo and experiencing no improvement, sought relief of their symptoms elsewhere. On the other hand, many patients complained of nausea with AE-1 and AE-2, and although hot flashes and other symptoms were relieved, some felt that "the medicine just didn't agree" with them, so stopped medication after the first few doses. In spite of these

Mrs. L.C.M., w.f. 39. Menopause. Hot flashes and nervousness.
Smear 2 plus. (Hysterectomy.)

AE	1	2	3	4	
June	X				Satisfactory relief of symptoms. Nervous.
July		X			Better than AE-1, less nervous. Smear 3–4 plus.
Aug.			X		Better than AE-1 or AE-2.
Sept.				X	Very well; no change.
Oct.				X	Very well; no change.
Nov.				X	Not so well. Backache. Smear 3 plus.
Dec.				X	Complete return of symptoms.
Jan.				X	Worse than ever. Smear 2 plus.
Feb.				X	Nervous. Severe hot flashes. Smear 2 plus.
Mar.	X				Relief of all symptoms. Calm. Smear 4 plus.

Patient at first obtained satisfactory results with AE-1, 2, 3 and 4, administered in that order, but symptoms recurred on continued therapy with AE-4 and were entirely relieved by AE-1.

FIGURE 4

difficulties many patients found a personal interest in cooperating when advised that many preparations were available to relieve them, but an attempt was being made to determine which type of therapy proved most effective in their individual cases.

Most patients found AE-1 or AE-2 satisfactory whether or not they had previously received AE-3 or AE-4, and repeated courses in different sequence were necessary to determine which gave the best results. Obtaining complete relief of symptoms with one preparation, some patients were reluctant to change to another. Prolonged effects of one course of therapy often made comparison difficult. "Lag time" in effect of therapy was

occasionally disturbing. For instance, 10.6 per cent of the patients who received AE-1 as an initial course of therapy stated that they noticed only moderate or very little improvement of symptoms at first. Then when given AE-4 as a subsequent course of therapy some noted better results, which later proved to be a carry-over effect of the AE-1. If AE-4 were continued, however, symptoms practically always recurred, then disappeared

Mrs. H.G.O., w.f. 44. Menopause. Hot flashes—severe (previously controlled with estrogens but had severe bout of uterine bleeding following estrogen therapy).

AE	1	2	3	4	
June	X				Complete relief. Excessive withdrawal bleeding.
July					
Aug.		X			Complete relief. Almost normal period.
Sept.			X		Recurrence of symptoms, no relief.
Oct.				X	Hot flashes worse than ever before.
Nov.		X			Complete relief. Normal withdrawal period.
Dec.			X		No relief, recurrence of symptoms.
Jan.				X	No relief. Hot flashes severe (20–30 per day).
Feb.	X				Complete relief of symptoms.

Patient preferred AE-2 because withdrawal bleeding was controlled and was much less than with AE-1. Both preparations gave equally good results as far as amelioration of hot flashes was concerned.

FIGURE 5

promptly when AE-1 was substituted for AE-4 (Fig. 4). In many instances in which patients could not give an opinion as to the most effective preparation it was necessary to repeat the different preparations in varying sequence after return of symptoms. The statistical data and the data on the comparative effectiveness of these preparations as shown in the figures were determined for final analysis in the manner described above.

Although it has been stated that the use of the vaginal smear appears to have little value as a routine procedure in determination of symptom response (10, 11) we noted in this series a definite correlation between relief of true menopausal symptoms and maturation of the cells in the vaginal

smear, even though the actual medication being administered was not known.

The incidence of nausea in this series approximated our previous experiences with stilbestrol therapy (13); however, during the study no effort was made to determine the optimal dosage for each individual because the dosage schedule was standard for comparative purposes.

The comparative subjective response of 31 menopausal patients to the different preparations is presented in Table 1. These patients were chosen because most of them received all four of the preparations and were able to give a reliable impression of each. The results reported are final impressions gained after repeated courses of therapy in varying sequence. The degree of subjective response is indicated by the symbols "0" to "++++." The latter indicates complete relief of hot flashes, nervousness, formication, and associated symptoms; "0" indicates no improvement in symptoms, or a recurrence of symptoms during therapy.

In general, patients felt better and were relieved of symptoms while taking either AE-1 or AE-2; most patients were partially relieved of symptoms by AE-3, and very few responded favorably to AE-4.

From an analysis of this clinical study we were able to meet satisfactorily the challenge of determining the content of each of the AE preparations. We reported, and correctly so, to Dr. D. C. Hines of the Eli Lilly Research Laboratories, that our clinical evaluation indicated that AE-1 contained diethylstilbestrol alone, that AE-2 contained both diethylstilbestrol and methyltestosterone, that AE-3 was methyltestosterone, and that AE-4 was the placebo.

Analysis of Response to Individual Preparations

AE-1: Diethylstilbestrol 0.25 mg.

Satisfactory relief of hot flashes and other menopausal symptoms was reported by 96.9 per cent of all patients who received AE-1. In every instance in which an estrogen deficiency was reflected in the vaginal smear before therapy there was maturation of the cells and evidence of estrogenic response to therapy with AE-1. Nausea accompanied therapy in 30.5 per cent of cases. This was attributed to therapy only if it disappeared when AE-1 was discontinued and then recurred when therapy was resumed. A few patients discontinued AE-1 because of excessive nausea. Uterine bleeding followed therapy in 34.2 per cent of the patients who had an intact uterus. The bleeding amounted only to slight spotting in most instances; however, it occasionally resembled a menstrual period, lasting four or five days. In only an occasional instance was the amount of bleeding so excessive that other hormonal measures had to be taken to control it (Fig. 5).

AE-2: Diethylstilbestrol 0.25 mg. and methyltestosterone 5.0 mg.

Complete relief of hot flashes and associated menopausal symptoms was reported by 89.6 per cent of all patients who received this combination of estrogen and androgen therapy. Improvement in the hypoestrogenic vaginal smear was a constant finding, and in those patients who had previously shown maturation from an atrophic (castrate) state to a mature estrogenic vaginal mucosa, there was no marked regression during AE-2 therapy. Although over 90 per cent of all patients who received both AE-1 and AE-2 reported complete relief of menopausal symptoms with both preparations, many (66.6 per cent) of these same patients stated a preference for AE-2 because of the additional increase in "well being." Increased libido was reported by 23.5 per cent of patients. Therapy with AE-2 was followed by vaginal bleeding in 30.5 per cent of patients with an intact uterus. The bleeding was considerably less in amount than that reported by the same patients following a course of AE-1. The incidence of nausea was also less with this preparation than with AE-1, and was reported by only 4 per cent of patients as compared to almost 1 out of 3 with AE-1.

In recapitulation, AE-2, the combination of diethylstilbestrol and methyltestosterone, gave essentially the same excellent relief of hot flashes, headaches, formications, insomnia and nervousness as AE-1, but had the additional advantages of significantly lower incidence and diminished amount of breast turgidity, pelvic congestion and nausea, and a greater incidence of increased libido. Although the incidence of bleeding following therapy was essentially the same as that following AE-1, the amount of bleeding after AE-2 was strikingly less. Mild acne, hoarseness, or increase in facial hair growth was reported in 13.2 per cent of cases with this dosage schedule. In all cases the untoward effects of androgen therapy were transient and regressed shortly after therapy was discontinued.

AE-3: Methyltestosterone 5.0 mg.

Some very interesting results were obtained with AE-3. Whereas the results with AE-1 and AE-2 were generally satisfactory, symptomatic response to AE-3 varied widely. About one-fourth (23.6 per cent) of the patients who received AE-3 reported no relief of hot flashes or other symptoms. Approximately the same number, however, (23.5 per cent) reported excellent results and complete relief of hot flashes. Essentially half (52.9 per cent) reported a lowered frequency and decreased severity of hot flashes, or partial improvement of symptoms. Final analysis of these patients confirmed the impression that AE-3 (methyltestosterone) completely relieved the symptoms of slightly less than one fourth of patients when given as initial therapy. Half of the patients who received AE-3 as their first course of therapy realized partial relief of symptoms. The vaginal

smear as a rule was maintained in unchanged status with AE-3 therapy, that is to say, a castrate smear remained castrate, and a mature smear showed little or no regression. In general, both the estrogenic smear and alleviation of symptoms acquired by previous therapy with estrogen (AE-1 or AE-2) were maintained by therapy with AE-3. In other words, there was a tendency for methyltestosterone to perpetuate the satisfactory results of previous estrogen therapy.

Essentially the same incidence (12.8 per cent) of acne, hoarseness, or hirsutism was noted with AE-3 as with AE-2; however, 42 per cent of patients reported an increase in libido, and only 5.2 per cent experienced nausea attributable to medication. Uterine bleeding attributable to AE-3 therapy was observed in only 1 patient.

AE-4: Placebo tablets

Response to therapy with AE-4 was in general disappointing. Although 7.1 per cent of the patients in the entire series stated that AE-4 relieved hot flashes, only 1 out of 14 reliable menopausal patients who were given AE-4 as the initial course of therapy reported relief of hot flashes. Many patients who had already been relieved with AE-1 or AE-2 reported that AE-4 was satisfactory, but with continuation of AE-4 therapy, hot flashes, nervousness, and other symptoms returned. Some reported vaginal bleeding during the first two weeks of therapy, and this was in every instance attributable to withdrawal of estrogen (AE-1 or AE-2) therapy. Increased libido was reported by 1.8 per cent of patients, and 9.1 per cent reported some improvement of hot flashes. Of all patients who received AE-4 in this series, 83.8 per cent either observed no improvement of symptoms which were present, or noted return of symptoms during therapy. No improvement in vaginal smears was observed, but many showed regression from an estrogenic response which had resulted from previous estrogen therapy. Nausea attributed by patients to medication was reported in 3.6 per cent of cases.

CONCLUSIONS

1. Two hundred and eighty-four courses of therapy with four different preparations were administered in varying sequence to 102 patients with symptoms of the menopause. These preparations, labeled "AE-1," "AE-2," "AE-3," and "AE-4," contained diethylstilbestrol (0.25 mg.), a combination of methyltestosterone (5.0 mg.) and diethylstilbestrol (0.25 mg.), methyltestosterone (5.0 mg.) alone, and a placebo, respectively. The specific content of each preparation was not made known to us for this study so that suggestion and pre-existing preference were circumvented in evaluation of these preparations.

2. Effect on symptoms and on vaginal smear:

a) Satisfactory relief of hot flashes and other menopausal symptoms was reported by 96.9 per cent of all patients who received AE-1, and maturation of the cells in the vaginal smear was a constant observation.

b) Therapy with AE-2 gave the same excellent relief of hot flashes and associated menopausal symptoms in 89.6 per cent of cases, and improvement in the hypoestrogenic vaginal smear was a constant finding.

c) Symptomatic response to therapy with AE-3 varied widely. Satisfactory relief of symptoms was reported by 23.5 per cent of patients with AE-3 therapy. A moderate degree of amelioration of symptoms was reported by approximately half (52.9 per cent) of the patients, and 23.6 per cent of patients experienced no relief of hot flashes or other symptoms. In general there was no cytologic change in the vaginal smear during AE-3 therapy; that is to say, a castrate smear remained castrate, and a mature smear showed little or no regression. Both symptomatology and vaginal cytology which had been improved by previous estrogen (AE-1 or AE-2) therapy were maintained by subsequent therapy with AE-3.

d) Therapy with AE-4 was entirely unsatisfactory in the treatment of vasomotor symptoms in the true menopausal patient. Although 7.1 per cent of patients stated that AE-4 relieved hot flashes, only 1 out of 14 reliable menopausal patients who were given AE-4 as the initial course of therapy reported any relief of symptoms. During therapy with AE-4 83.8 per cent of patients reported either no improvement, or recurrence of symptoms which were previously relieved by AE-1 or AE-2 therapy. There was no improvement in vaginal smears, but many cells showed regression from maturation previously attained with estrogenic therapy.

3. Untoward effects of therapy:

a) Nausea accompanied therapy with AE-1 in 30.5 per cent of patients with the dosage schedule employed in this study. Uterine bleeding followed therapy in 34.2 per cent of the patients with an intact uterus.

b) Nausea occurred in only 4 per cent of patients with AE-2 therapy. Uterine bleeding followed therapy with AE-2 in 30.5 per cent of patients with an intact uterus, but in general was less in amount than that following AE-1. Mild acne, hoarseness, or increase in facial hair growth was observed in 13.2 per cent of patients while taking AE-2. These untoward effects of androgen therapy were in all cases transient and regressed shortly after therapy was discontinued.

c) Nausea was reported by 5.2 per cent of patients receiving AE-3 therapy. Uterine bleeding attributable to therapy was seen in only 1 case. Approximately the same incidence (12.8 per cent) of acne, hirsutism, or hoarseness was noted with AE-3 as with AE-2.

d) There were no untoward effects of therapy with AE-4 other than those attributable to a return of symptoms following the "carry-over" effects of previous therapy with the other preparations.

4. Increased libido was reported by 12.3 per cent of patients with AE-1, 23.5 per cent of patients with AE-2, and 42 per cent of the patients who received AE-3.

5. Of all patients who received all four of the preparations, 91.6 per cent stated a preference for either AE-1 or AE-2. Of these, 66.6 per cent believed AE-2 superior to AE-1 because of increased well-being and libido, less uterine bleeding, less nervousness and nausea and fewer headaches. The patients who observed hoarseness, acne, or increase in facial hair growth gave these factors as a reason for their preference for AE-1, although both preparations satisfactorily controlled menopausal symptoms.

6. From our clinical observations we correctly determined the specific content of each of the four preparations.

7. The combination of an estrogen and an androgen, in general, gave the best results. It appears too, that androgens and estrogens given in combination in this fashion modify the specific action of each other but do not neutralize one another, since the development of mild hoarseness, hirsutism and acne occurred along with uterine bleeding and maturation of the cells in the vaginal smears.

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STUDIES OF URINARY CORTICOSTEROID BY A METHOD PERMITTING ANALYSIS OF STEROIDS POORLY SOLUBLE IN WATER. I. NORMAL ADRENAL FUNCTION*

CHARLES W. LLOYD, M.D. AND JULIA LOBOTSKY, M.S.

From the Departments of Obstetrics, Medicine, and Physiological Chemistry, Syracuse University College of Medicine, Syracuse, N. Y.

MEASUREMENT of urinary corticosteroid by the method of Daughaday and co-workers (1) for estimation of formaldehyde-forming steroids or by the method of Talbot *et al.* (2) for copper-reducing substances involves partition of the urinary residue between benzene and water. Since only the steroids in the water fractions are measured, those corticosteroids which have solubility properties similar to those of desoxycorticosterone and are poorly soluble in water are not measured by these methods. The phosphomolybdic acid reduction method of Heard, Sobel, and Venning (3) and the Tompsett and Oastler (4) modification of the method of Talbot *et al.* permit determination of water-insoluble steroids. However, the possibility of nonspecificity for these procedures which determine reducing power is considered greater than for the periodic acid oxidation method (5). Therefore, a method has been developed which measures the formaldehyde formed by periodic acid oxidation in a solvent permitting solution of steroids poorly soluble in water, and thus permitting recovery of a formaldehyde-forming material in human urine following administration of desoxycorticosterone. It is similar to the method described by Corcoran and Page (6); and since it measures those steroids which are water-soluble as well as those which are poorly soluble in water, the material determined is called the "total corticosteroid." That ma-

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The desoxycorticosterone acetate used in these studies was either Cortate (Schering) or Percorten (Ciba). We wish to thank Dr. E. Oppenheimer and Mr. F. E. Houghton of the Ciba Company for generously supplying the Percorten used in the study shown in Figure 1 and the macrocrystalline suspension of DCA used in treatment of some of the patients. The Adrenal Cortical Extract and Lipo-Adrenal Cortex used in some of these studies was supplied through the courtesy of Dr. Harold Hailman of the Upjohn Company.

We wish to thank Dr. W. W. Westerfeld for his help in developing the methods used in these studies.

terial which is passed from benzene to water by a technic similar to that of Daughaday *et al.* (1) is called the "water-soluble corticosteroid," and that material which remains in the benzene phase is called "corticosteroid poorly soluble in water." This report concerns studies of the excretion of the "total corticosteroid" and in some instances of the "water-soluble corticosteroid" by normal adults. The subsequent report (7) concerns the excretion of these materials by subjects with adrenal insufficiency.

METHODS

Urine collections were made with refrigeration or chloroform preservation during the collection period. Urines were extracted the day of completion of the collection because bacterial contamination of the urine tends to cause increased yields of formaldehyde, and none of the commonly used preservatives has been found capable of preventing this increase.

Urinary 17-ketosteroids were measured by a modification of the method of Callow and Callow (8) or by the method of Drekter *et al.* (9). Sodium and potassium were measured with a flame photometer.

Estimation of total corticosteroid

Extraction: An aliquot of urine measuring between 200 and 400 ml., the amount being varied inversely with the predicted corticosteroid level, was acidified to pH 1 with hydrochloric acid. The extraction was carried out three times with the total amount of chloroform being equivalent to the volume of the urine aliquot.[1] Emulsions were broken by centrifugation and when necessary by freezing, between each extraction. The chloroform was reduced under vacuum at a temperature below 60° C. to about 200 ml., cooled in the icebox and then washed three times with a total of 200 ml. of cold 0.1 N sodium hydroxide and three times with a total of 200 ml. of water.[2] The combined alkali and water washings were extracted once with 50 ml. of chloroform. The total chloroform extract was reduced to dryness *in vacuo* on a water bath at a temperature below 60° C. The residue was desiccated overnight. Residues may be stored in a desiccator for several months.

Oxidation:[3] The residue was dissolved in 5 ml. of glacial acetic acid. A 3 ml. aliquot

[1] The use of constant proportions of solvent to urine is of importance since complete extraction is impractical because of the extremely large volumes of solvent required.

[2] The alkali and water washes, which were not included in the original method of Daughaday *et al.*, remove a large amount of formaldehyde-forming nonsteroidal material such as glucose.

[3] 1. Glacial acetic acid, fractionally distilled (assay before using).

2. Periodic acid reagent:
   Periodic acid (C.P., Amend Drug & Chemical Co., Inc., New York) 0.01 M in 0.15 M H_2SO_4.

3. Stannous chloride:
   6 Gm. in 10 cc. hot conc. HCL; dilute to 100 ml. with water.

4. Sodium bisulfite:
   4 Gm. in 100 cc. water.

(*Continued next page*)

was put in a round-bottom distilling flask. If an amount less than 3 ml. was used, the volume of the solution was made up to 3 ml. by the addition of glacial acetic acid. Two ml. of periodic acid solution were added, the flask was shaken and allowed to stand at room temperature for forty-five minutes. One ml. of stannous chloride solution was now added, the solution was shaken, and then 4 cc. of water were added, making the total volume 10 ml. This solution was distilled through a microcondenser of the type described by Stotz (11) (Macalaster-Bicknell) and 8 ml. of the distillate were collected in a graduated 15 cc. centrifuge tube containing 1 ml. of sodium bisulfite solution. Tubes were stoppered and inverted several times. A reagent blank using 3 ml. of glacial acetic acid was included. A standard solution of desoxycorticosterone in glacial acetic acid was routinely measured with each series of determinations.

Color development: Four ml. of distillate were placed in a 15 ml. graduated centrifuge tube. Duplicate determinations were always made. Five ml. of chromotropic acid reagent were added and the tubes shaken. The tubes were heated for thirty minutes in a boiling water bath. To insure thorough mixing, the tubes were rotated vigorously after being in the water bath for five minutes. The tubes were cooled to room temperature under running tap water. The volume was made up to 10 ml. with 15 N sulfuric acid. Absorption of light was measured in the Coleman spectrophotometer at a wave length of 550 mμ.

Calculations: The difference between the antilog of the spectrophotometer reading of the unknown and antilog of the blank reading was referred to a standard curve for formaldehyde.[4] The results are expressed as micrograms of formaldehyde formed from the corticosteroid excreted in twenty-four hours. The formaldehyde values were not converted to steroid equivalents because the number of moles of formaldehyde yielded varies, depending upon the side-chain configuration of the unknown steroid (13). Excretion may be expressed in terms of desoxycorticosterone equivalents by multiplying by a factor of 11.

Estimation of water-soluble corticosteroid

This procedure was sometimes performed in addition to the assay of "total corticosteroid." Twice as much urine was extracted, using a volume of chloroform equal to the urine volume. The chloroform extract was evaporated to 200 ml. Alkali and water washings were carried out as previously described. The final chloroform fraction was divided into two equal parts and evaporated to dryness. One of the residues was used for assay of "total corticosteroid" as described above. A benzene-to-water partition was carried out on the other residue.

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5. Chromotropic acid solution:
   5 Gm. Eastman Kodak chromotropic acid (1,8-dihydroxynaphthalene-3,6 disulfonic acid) in 100 cc. distilled water. Store in ice box in brown glass bottle. Discard when dark. Purify chromotropic acid before use by the method of Boyd and Logan (10).
6. Chromotropic acid reagent:
   Make up freshly each day; 4 ml. of chromotropic acid solution to 100 ml. with cold 15 M H_2SO_4.

[4] Hexamethylenetetramine was used as the source of formaldehyde after the method of MacFadyen (12). Paraformaldehyde was unsatisfactory for this purpose.

Benzene-to-water partition: The benzene-to-water partition was slightly modified from that described by Daughaday, Jaffe and Williams (1). The residue was dissolved in 1 ml. of benzene and transferred to a 15 ml. centrifuge separatory funnel (Macalaster-Bicknell). The flask was washed twice with 0.5 ml. of benzene in order to complete the transfer. The benzene was extracted three times with water, with volumes of 5 ml., 3 ml., and 2 ml. for successive washings. Emulsions were broken by centrifugation at a low speed. The water extracts were pooled and the volume adjusted to 10 ml.

Oxidation: Three ml. of glacial acetic acid and 2 ml. of periodic acid were added to 4 ml. of the water fraction in a round-bottom distilling flask. Distillation and color development were carried out in the same manner as for the "total corticosteroid." Whenever a difference between "water-soluble" and "total corticosteroid" values on the same specimen was found, the fraction which remained in the benzene was measured by evaporating the benzene and dissolving the residue in glacial acetic acid, after which the procedures described above were carried out on it. It was only when an amount of corticosteroid in the benzene fraction was found which was comparable to the difference between the "total" and "water soluble" fractions that the difference was considered significant.

RESULTS

Corticosteroid excretion of adult subjects with presumably normal adrenal function

In Table 1 are presented the corticosteroid values for 33 twenty-four-hour urine specimens collected from 11 males with presumably normal adrenal function. These subjects were from 16 to 50 years old. The values for total corticosteroid ranged from 17 to 60 micrograms of formaldehyde in twenty-four hours. Included in the data for subject M-1 is one value of 74 micrograms in twenty-four hours, to demonstrate the response of the normal male to excessive hydration. In Table 2 are presented the corticosteroid values for 36 twenty-four hour specimens collected from 20 females with presumably normal adrenal function. The range during normal conditions for total corticosteroid formaldehyde in this group is from 18 to 62 micrograms in twenty-four hours. The value of 80 micrograms for twenty-four hours for subject F-1 was obtained during diuresis induced by water ingestion. A positive correlation between corticosteroid value and urine volume is present to the extent that a low corticosteroid has never been found in a urine of large volume. The high values for subjects M-11 and F-19 were found during the time that the subjects were under the psychologic stress of an important examination. On a few specimens, water-soluble corticosteroids were run simultaneously with the total corticosteroid and in most of the normal individuals the water-soluble fraction was essentially equivalent to the total corticosteroid, although in 3 subjects (M-8, F-6, F-10) a considerable amount of material poorly soluble in water was found.

TABLE 1. CORTICOSTEROID EXCRETION BY NORMAL MALE SUBJECTS

Subject	Total formaldehyde, γ per 24 hrs.	Water-soluble formaldehyde, γ per 24 hrs.	Remarks
M- 1	23		Normal conditions
	36		Normal conditions
	38		Normal conditions
	39		Normal conditions
	29		Normal conditions
	44		Normal conditions
	30		Normal conditions
	40		Normal conditions
	30		Normal conditions
	39		Normal conditions
	41		Normal conditions
	74		Water diuresis; urine vol. 5200 cc./24 hours
M- 2	31		Normal conditions
	45	48.0	Normal conditions
M- 3	30		Normal conditions
M -4	60		Normal conditions
M- 5	43		Normal conditions
M- 6	17	18.0	Normal conditions
	32	31.0	Normal conditions
	46		Normal conditions
M- 7	32		Normal conditions
M- 8	52	29.5	Normal conditions
	54		Normal conditions
	44	38.4	Normal conditions
	32	26.0	Normal conditions
	40	46.0	Normal conditions
	30	27.0	Normal conditions
M- 9	46		Normal conditions
	25		Normal conditions
	21		Normal conditions
M-10	21	17.3	Normal conditions
M-11	37		Normal conditions
	79		Psychologic stress; urine vol. 5800 cc./24 hours

In Figure 1 is shown the daily corticosteroid excretion of a 42-year-old male with normal adrenal function to whom Lipo-Adrenal Cortex and desoxycorticosterone acetate (hereafter called DCA) were given. This patient was admitted to the hospital because of vague pains in both shoulders. No evidence of disease was found by physical, roentgenologic or

TABLE 2. CORTICOSTEROID EXCRETION BY NORMAL FEMALE SUBJECTS

Subject	Total formaldehyde, γ per 24 hrs.	Water-soluble formaldehyde, γ per 24 hrs.	Remarks
F- 1	46		Normal conditions
	43		Normal conditions
	25		Normal conditions
	80		Diuresis; urine vol. 7200 cc./24 hours
F- 2	47		Normal conditions
	47		Normal conditions
	28		Normal conditions
	53		Normal conditions
F -3	32		Normal conditions
	30	28	Normal conditions
F- 4	30	28	Normal conditions
	41	28	Normal conditions
F- 5	18		Normal conditions
	26		Normal conditions
F- 6	27	31	Normal conditions
	55	40	Normal conditions
F- 7	24	26	Normal conditions
	31		Normal conditions
F- 8	42		Normal conditions
F- 9	24	29	Normal conditions
F-10	31	18	Normal conditions
	60		Normal conditions
F-11	62		Normal conditions
	33		Normal conditions
	54		Normal conditions
	41		Normal conditions
F-12	37		Normal conditions
F-13	53		Normal conditions
F-14	58		Normal conditions
F-15	33		Normal conditions
F-16	46		Normal conditions
F-17	37	37	Normal conditions
F-18	54	45	Normal conditions
	48	54	Normal conditions
F-19	82		Psychologic stress; urine vol. 2960 cc./24 hours
	38	32	Normal conditions
F-20	56	59	Normal conditions

laboratory examinations. Throughout the entire study the salt intake was maintained at 4.8 Gm. daily except for the twentieth day, at which time it was increased to 10 Gm. for one day. In the afternoon of the seventh

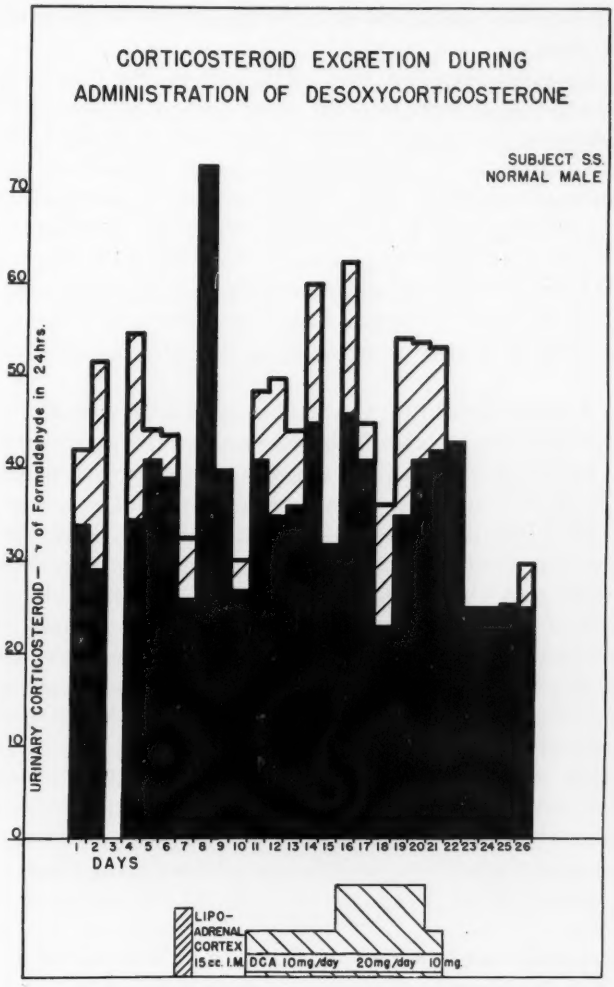

FIG. 1. Corticosteroid excretion of a 42-year-old man with presumably normal adrenal function. The total corticosteroid is shown by the upper bar. The solid bar represents the freely-water-soluble fraction.

day the patient was given 15 cc. of Lipo-Adrenal Cortex. On the eleventh day, injection of 10 mg. of DCA daily was begun. On the sixteenth day DCA was increased to 20 mg. During the entire study the patient remained subjectively and objectively well. No change in the patient's weight or blood pressure occurred until the twentieth day when the salt was increased, at which time there was a weight gain of 2 pounds and an increase of 40 mm. of mercury in the systolic blood pressure. The salt was thereafter

restricted to 4.8 Gm. daily and only 10 mg. of DCA was given on the twenty-first day.

The corticosteroid excretion was fairly high during the 5-day control period. A sharp rise in corticosteroid excretion lasting twenty-four hours occurred following the administration of the Lipo-Adrenal Cortex. Very little, if any, increase in corticosteroid excretion occurred during the administration of the DCA. The average of the corticosteroid values for control days 1 through 6 is 44 γ in twenty-four hours, whereas the average of the values for the twelve days during which DCA was given is 48 γ in twenty-four hours. Following cessation of DCA, a drop to a lower level of corticosteroid excretion occurred. This lower level of activity was still present when the study was terminated on the fifth day after withdrawal of DCA.

On several occasions during the control period there was a significant difference between the water-soluble fraction and the total corticosteroid. During the period in which DCA was given by daily injection, the patient continued to excrete material which was poorly soluble in water. When the dose of DCA was decreased from 20 mg. to 10 mg. daily, the decrease in corticosteroid which occurred was almost entirely the result of the disappearance from the urine of the fraction poorly soluble in water. The cessation of administration of DCA on the twenty-second day resulted in a further considerable decrease in corticosteroid excretion and a disappearance of the fraction poorly soluble in water for the three days during which the corticosteroid remained low. On the last day of the study, a small amount of material poorly soluble in water was found. A moderate salt retention occurred during the period of desoxycorticosterone administration and a marked natriuresis occurred during the period of withdrawal of DCA. This negative sodium balance was associated with the disappearance of the corticosteroid poorly soluble in water from the urine.

DISCUSSION

At present sufficient data are not available to allow an evaluation of the significance of the presence of poorly-water-soluble as well as freely-water-soluble corticosteroids in the urine. Daughaday, Williams and Jaffe (1) consider that "most of the formaldehyde forming compounds entered the aqueous fraction" during the benzene-to-water partition, and Tompsett and Oastler (4) state that "the ketonic reducing substances in urine are mostly, if not entirely, water-soluble." No poorly-water-soluble material was found in the majority of the urines in this study, but significant differences between the total corticosteroid and the water-soluble fractions were found in urines of 3 presumably healthy subjects.

When the total and water-soluble corticosteroid are compared by the

methods used in this study, the water-soluble corticosteroid value is usually equal to, and often slightly higher than, the total corticosteroid value obtained by carrying out the oxidation in glacial acetic acid. This is probably due to a slightly more complete reaction when the steroid is oxidized in water. For this reason, the occasional corticosteroid which does not partition completely into water is all the more striking.

The disappearance of the material poorly soluble in water from the urine of the subject S.S. (Fig. 1) following discontinuance of DCA administration suggests that in this subject the exogenous desoxycorticosterone inhibited production of the fraction poorly soluble in water. No unusual metabolic activity was evident in the 3 presumably normal subjects having this material in their urine and at present no functional correlations can be made.

The study carried out on S.S. (Fig. 1) furnishes evidence of inhibition of presumably normal adrenal function by exogenous desoxycorticosterone, since administration of DCA caused relatively little increase in urinary corticosteroid and removal of the exogenous steroid was followed by a very low rate of excretion. The major portion of the decrease in corticosteroid was at the expense of the material poorly soluble in water; therefore, it seems probable that this factor was principally inhibited by the administered DCA.

From the data included in this study, and from the studies reported in the subsequent paper (7) it is possible to make some deductions about recovery of administered cortical steroids. The amount of desoxycorticosterone contained in the DCA administered was calculated and the percentage of the injected desoxycorticosterone excreted in the urine was determined. Similar calculations were carried out when Lipo-Adrenal Cortex was the material injected, based on an estimated 1 to 2 milligrams of $C_{21}O_5$ cortical steroids in each cubic centimeter of the solution given. Patients with adrenal insufficiency described in the subsequent paper excreted from 1 to 3 per cent of injected desoxycorticosterone or of cortical steroids of Lipo-Adrenal Cortex. Subject S.S. (Fig. 1) excreted approximately 2 per cent of injected DCA. These calculations indicate that under usual circumstances cortical steroids are effectively utilized or destroyed. In contrast, a patient with adrenal insufficiency who received a large overdose of DCA excreted 10 per cent of the injected desoxycorticosterone. This possibly indicates a failure to inactivate steroid when the organism was overwhelmed. This patient will be described elsewhere (7). As an indication of the range of activity of the normal adrenal cortex, calculations based on a normal corticosteroid excretion rate of 18 to 60 micrograms of formaldehyde in twenty-four hours indicate that the normal gland probably secretes steroid equivalent to 10 to 35 mg. of DCA daily.

It is probable that under conditions of stress the gland is capable of secreting steroid equivalent to at least several hundred milligrams of DCA daily. Obviously these figures have no absolute value, but are presented in an attempt to indicate the potentialities of the normal gland.

SUMMARY

1. A method for determination of corticosteroid is described which utilizes glacial acetic acid as the solvent in which periodic acid oxidation forms formaldehyde. Before oxidation, a benzene-to-water partition is carried out on a residue from the same urine specimen. The fraction assayed in glacial acetic acid is considered to be the "total corticosteroid." The fraction partitioned from benzene to water is considered the "freely-water-soluble corticosteroid." By difference, the "corticosteroid poorly soluble in water" is determined.

2. No sex difference in "total corticosteroid" excretion is detectable in normal adults. In most instances, the "total corticosteroid" is water-soluble. Occasionally a specimen contains a significant amount of "corticosteroid poorly soluble in water." The significance of this material is not known.

3. Administration of DCA to a subject with presumably normal adrenal function produced very little increase in corticosteroid. Following withdrawal of the DCA a considerable drop in corticosteroid occurred. The "poorly-water-soluble corticosteroid," which was present in greater than usual amounts during the pretreatment control period, did not increase significantly during the time when DCA was given, but it disappeared completely for three days after the withdrawal of DCA.

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THE EXCRETION OF 17-KETOSTEROIDS, 11-OXYCORTICOSTEROIDS AND "11-DESOXYCORTICOSTEROIDS" IN PATIENTS WITH BRONCHIAL ASTHMA

DESYR HIOCO, M.D.* AND MAX SAMTER, M.D.

From the Allergy Unit, Department of Medicine, University of Illinois College of Medicine, Chicago, Illinois

IN 1945, Rackemann (1) reported metabolic studies on a patient with bronchial asthma due to "depletion," a nonspecific term introduced by him which designates bronchial asthma associated with exhaustion, chronic infection or emotional stress. In his report he writes:

"Dr. Albright pointed out that the man had suffered repeated insults to his system and so might be compared with animals which had been exposed to repeated trauma until they were in the resistant or counter-shock stage of the "alarm reaction" as described by Selye and his co-workers. Dr. Albright found that this man excreted in the urine only 5.5 mg. of 17-ketosteroids in one day in place of the normal 15 mg., and he pointed out the probability that the patient suffered from a marked disturbance in the function of the adrenal cortex."

In view of the potential importance of this observation, it seemed necessary to study a series of patients with bronchial asthma in an attempt to establish whether the reported decrease in the excretion of 17-ketosteroids was an isolated finding or an essential metabolic disorder of patients suffering with allergic diseases.

METHODS

For the determination of 17-ketosteroids in urine, the method of Cahen and Salter (2) was employed. The results are expressed in milligrams of androsterone per twenty-four hour period.

Studies on the definition of cortical hormone metabolites in the urine have been carried out by Fieser and his co-workers (3). Partition between water and benzene appears to increase the specificity of the determination (Talbot and co-workers (4)). In the present studies, estimations of corticosteroids were carried out by the modification of the Daughaday (5) method, based on the qualitative measurement of formaldehyde liberated by the oxidation of urinary extracts with periodic acid. The estimation of formaldehyde in biologic fluids by chromotropic acid has been described by MacFadyen (6).

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* Since the completion of this investigation, Dr. Hioco has returned to France. His present address is: 12 Rue Lagrange, Escantpont par Fresnes, Escant, Nord, France.

With periodic treatment each mole of desoxycorticosteroid yields one mole of formaldehyde; for every mole of 17-hydroxycorticoid two moles of formaldehyde result (10). We employed the factor of 0.5 given by Daughaday and have arbitrarily expressed the results in milligrams of corticoid per twenty-four hour period. Throughout this paper, the formaldehyde-

TABLE 1. EXCRETION OF 11-OXYCORTICOSTEROIDS, "11-DESOXYCORTICOSTEROIDS," AND 17-KETOSTEROIDS IN HEALTHY SUBJECTS

Subject No.	11-Oxycorticosteroids	"11-Desoxycorticosteroids"	17-Ketosteroids	Ratio $\frac{\text{11-Oxy}}{\text{11-Desoxy}}$
1	1.42	0.21	10.2	6.7
2	1.24	0.25	8.1	4.9
3	1.14	0.18	—	6.3
4	1.42	0.15	—	9.4
5	1.63	0.29	11.0	5.6
6	1.29	0.10	9.2	12.9
7	1.31	0.15	12.3	8.7
8	1.40	0.24	15.6	5.8
9	1.22	0.21	10.8	5.8
10	0.94	—	8.4	—

producing compounds from the water phase will be called 11-17 oxycorticoids, and those from the benzene phase "desoxycorticoids." (For details, see Appendix.)

SELECTION OF PATIENTS

Ten healthy subjects and 22 persons ill with bronchial asthma were selected for the study; of the latter, 14 were women and 8 were men.

Patients suffering from bronchial asthma can be divided into those who have a clearly defined allergic origin for their disease and those who are "non-allergic." It is conceivable that the "non-allergic" group is so labeled because present methods of clinical investigation fail to reveal an allergic factor in their illness. On the other hand, there is increasing evi-

TABLE 2. EXCRETION OF 11-OXYCORTICOSTEROIDS, "11-DESOXYCORTICOSTEROIDS" AND 17-KETOSTEROIDS IN 22 PATIENTS WITH BRONCHIAL ASTHMA

Patient	Sex	Allergic	Nonallergic	Severity	Duration (yrs.)	11-Oxycorticosteroids	"11-Desoxycorticosteroids"	17-Ketosteroids	Ratio $\frac{\text{11-Oxy}}{\text{11-Desoxy}}$
1. F.T.*	F		X	Mod.	5	0.74	0.19	5.9	3.8
2. C.R.	F	X		Sev.	31	0.52	0.18	6.4	2.8
3. R.P.	M	X		Mild	½	1.99	0.36	10.2	5.5
4. E.W.**	M	X		Sev.	15	0.78		10.2	
5. A.B.†	M	X		Sev.	25	1.56			
6. E.W.	M	X		Mod.	44	1.20	0.19	9.2	6.3
7. V.H.	F	X		Sev.	6	0.73	0.16	3.2	4.5
8. W.J.	M	X		Mod	20	1.85	0.32	10.3	5.7
9. E.T.	F	X		Mod.	3	0.80	0.14	8.7	5.7
10. W.P.	M	X		Sev.	30	0.82	0.19	8.2	4.3
11. L.W.	F	X		Mod.	6	2.01	0.41	7.4	4.9
12. A.L.‡	M	X		Sev.	2	1.61	0.30	12.1	5.3
13. B.R.	F	X		Mod.	8	0.42	0.14	6.2	3.0
14. F.Q.	F	X		Mod.	25	0.51	0.12	8.1	4.2
15. I.B.	F		X	Mild	20	1.21	0.21	9.2	5.7
16. B.C.#	M	X		Mild	14	1.10	0.12		9.1
17. M.O.	F	X		Mod.	5	1.40		10.1	
18. S.J.	F	X		Mod.	13	0.65			
19. H.J.	F	X		Sev.	11	1.12		9.6	
20. I.M.	F	X		Sev.	34	0.74	0.18		4.1
21. B.K.§	F		X	Mod.	15	0.55	0.15	6.1	3.6
22. T.S.	F	X		Sev.	44	0.55	0.15	6.1	3.5

* Osteoporosis; menopause.
** Moderate emphysema; bronchiectasis.
† Minimal cardiac involvement.
‡ Marked emotional disturbance.
# Sensitive to ragweed only. Only one attack of seasonal asthma during past year.
§ Moderate emphysema; bronchiectasis.

dence that "non-allergic" asthmatics may develop the clinical syndrome on some basis other than sensitization.

The allergic asthmatics were subdivided into patients with seasonal, and patients with perennial symptoms; the classification into seasonal or perennial allergy depends on the nature of individual exposure to specific allergens, but the mechanism of the disease is essentially the same. One of the seasonal patients (Table 2, No. 11) was examined while he had

bronchial asthma, the other (Table 2, No. 16) during a symptom-free interval.

Table 2 lists the asthmatic patients under study. The clinical aspects of the cases varied considerably. The duration of symptoms ranged from nine months to forty-four years; their degree, from mild to severe. Severity was determined by measuring impairment of breathing reserve (B.R.). This is a function of maximum voluntary ventilating capacity (M.V.V.C.—expressed in liters of air) and minute volume of breathing (M.V.—expressed in liters of air). It is calculated from the following formula: B.R. = M.V.V.C.—M.V./M.V.V.C. × 100 and, although not exact, permits a fair approximation of the clinical state of patients with bronchial asthma.

RESULTS

The urinary excretion of 17-ketosteroids, 11-oxycorticosteroids, and "11-desoxycorticosteroids" is shown in Table 1 and in columns 7, 8, and 9 of Table 2.

Statistical analysis of the data reveals no difference between healthy subjects and patients with bronchial asthma with regard to the amount of each substance excreted (Fig. 1). The large variations in daily output of

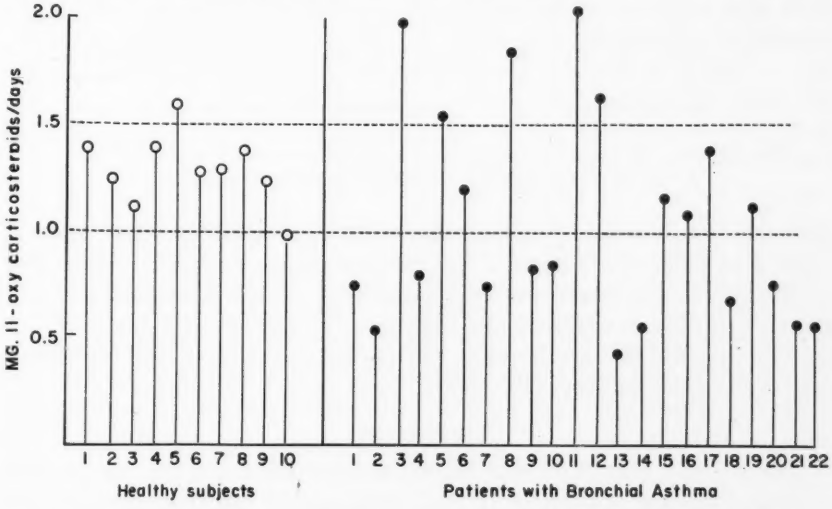
2.0
1.5
1.0
0.5
MG. 11-oxy corticosteroids/days
1 2 3 4 5 6 7 8 9 10
Healthy subjects
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Patients with Bronchial Asthma

FIG. 1. Excretion of 11-oxycorticosteroids (mg./day) of 10 healthy subjects and 22 patients with bronchial asthma.

hormones in the urine from one patient to another as well as from one healthy subject to another precluded obtaining significant differences between groups.

When the ratio of the excretion of 11-oxycorticosteroids to that of "11-desoxycorticosterone" (*see* 11-oxy/11-desoxy in the last columns of Tables 1 and 2) was calculated for normal subjects (M = 7.4) and for the asthmatic patients (M = 4.8), there appeared to be a suggestive difference in results (P = 0.07) (Fig. 2). Furthermore, it can be seen that the

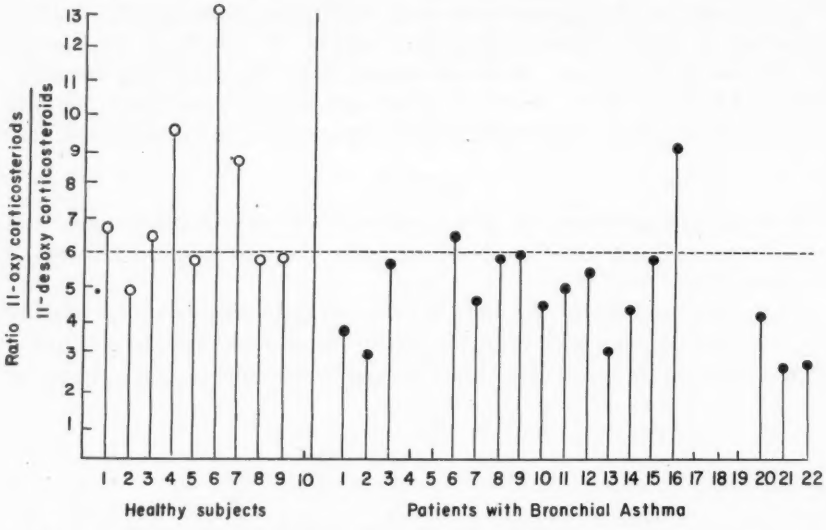

FIG. 2. Excretion ratio of 11-oxycorticosteroids/"11-desoxycorticosteroids" of 9 healthy subjects and 17 patients with bronchial asthma.

asthmatics with severe symptoms had the lowest ratios (M = 4.1) whereas those with moderate symptoms had the next lowest ratios (M = 4.7). The mean difference between the asthmatics with severe symptoms and the normal subjects was statistically highly significant (P = less than .01), as was the mean difference between the patients with moderate symptoms and the healthy subjects (P = .013).[1]

DISCUSSION

The concept that endocrine regulations participate in the mechanism of allergic disease, is not new. In 1923, Kepinow (7) had shown that guinea pigs with impaired adrenal function appeared to have exaggerated anaphylactic reactions. This observation has been adequately confirmed; for instance, in rats, which are notoriously resistant to sensitization, distinct anaphylactic symptoms developed when the animals were sensitized nine to fourteen days after bilateral adrenalectomy (Flashman (8)). These

[1] The numbers of the patients in Tables 1 and 2 correspond to those in Figures 1 and 2.

findings have been challenged by Wyman (9). Conversely, when the adrenal cortex is stimulated by injection of anterior pituitary extract, the resistance of experimental animals to anaphylactic shock is increased (Salominica and Kurzrok (10)). Dragstedt and his co-workers (11) demonstrated that although the administration of adrenal cortical extracts had no influence on sensitization, on anaphylaxis or on the titer of histamine subsequent to anaphylactic reactions, the severity of symptoms was diminished. Farmer (12) and Harkavy (13) correlated clinical experience with these experimental findings. It has been established in recent years that pituitary adrenal mechanisms, which release adrenal cortical steroids, can be set in motion by the injection of epinephrine hydrochloride. It appears that continuous stimulation of the adrenal cortex by prolonged administration of epinephrine increases the susceptibility of the experimental animal to sensitization and shock. Haag and co-workers (14) demonstrated in 1937 that guinea pigs sensitized to a weak antigen (powdered peas) could be shocked effectively if epinephrine was given at short intervals during the entire period of sensitization.

Several authors have attempted to correlate chemical changes with disturbed glandular function in allergy and to find a common denominator responsible for the "allergic trait" of man. Rush and Kenamore (15) demonstrated a marked alteration of potassium metabolism in patients with chronic urticaria. Correction of the assumed "cellular deficiency of potassium" by the administration of potassium chloride and a high-protein low-sodium diet resulted in improvement of the allergic manifestation. Stoesser (16), on the other hand, who treated children suffering from chronic bronchial asthma with potassium chloride, attributed the improvement to increased diuresis with resulting loss of sodium. His patients showed an exaggeration of symptoms after ingestion of sodium chloride or after administration of adrenal cortical extracts or after desoxycorticosterone acetate. Malone (17) and Black (18) reported that the fasting blood sugar level of allergic patients was lower than that of normal subjects. Abrahamson (19) called attention to the fact that diabetes and allergic diseases seldom co-exist. He concluded that hyperinsulinism plays an essential part in the metabolic mechanism of the allergic syndrome. We believe, however, that his data can be explained equally as well on the basis of hypofunction of the adrenal cortex as on the basis of hyperinsulinism.

The evaluation of our findings demands a brief discussion of the meaning and validity of the values obtained with the techniques which we have used for the determination of adrenal cortical metabolites. The footnote[2]

[2] (a) Excretion of 17-ketosteroids: Assuming a normal range of 17-ketosteroid excretion from 10 to 14 mgs. a day in men, and from 5 to 10 mgs. in women, the values which

clarifies the limitations of the method. It appears, however, that in patients with bronchial asthma of marked severity and long duration, the excretion of 11-oxycorticosteroids is relatively low, while the excretion of "11-desoxycorticosteroids" is relatively high; consequently, the ratio 11-oxycorticosteroids/"11-desoxycorticosteroids" is decreased in these patients.

We are not able to state whether the changes which have been found are specific for patients with chronic bronchial asthma or whether they occur in other prolonged and exhausting illnesses; nor is it known if they are the cause or the effect of the disease. It is tempting to suggest that bronchial asthma in these patients is due to a primary depletion of the adrenal cortex (Rackemann (1)), or to a deviation of the normal response of the adrenal cortex to stress (Selye (20)). It might be possible to arrive at further conclusions by determining whether or not the abnormal excretion of 11-oxycorticosteroids and "11-desoxycorticosteroids" can be corrected by stimulation of the pituitary-adrenal chain. Accordingly, we have studied the metabolic effect of epinephrine and adrenocorticotropic hormone on a number of patients; the results will be reported elsewhere.

SUMMARY

The daily excretion of 17-ketosteroids, 11-oxycorticosteroids and "11-desoxycorticosteroids" was measured in 10 healthy subjects and in 22 patients with bronchial asthma of different severity and duration, and the ratio of 11-oxycorticosteroids to "11-desoxycorticosteroids" (11-oxy/11-desoxy) was calculated.

The amount of 17-ketosteroids excreted by patients with bronchial asthma was normal. In patients with bronchial asthma of marked severity and long duration there was found a decrease in the excretion of 11-oxycorticosteroids and a relative increase in the excretion of "11-desoxycorticosteroids" when compared with healthy subjects. The ratio between 11-oxycorticosteroids and "11-desoxycorticosteroids" in these patients, by statistical analysis, was significantly decreased.

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are listed in column 9, Table 2 appear to be normal. Increasing doubt has been cast, however, on the significance of the excretion of 17-ketosteroids for the interpretation of adrenal function.

(b) Excretion of 11-oxycorticosteroids and "11-desoxycorticosteroids:" It is true that the "water phase" of Daughaday's method includes the 11-oxycorticosteroids, and the "benzene phase" the "11-desoxycorticosteroids." Undoubtedly, however, both fractions—particularly the benzene phase—also contain other steroids, and it is for this reason that we have placed the latter in quotation marks throughout this paper. Furthermore, one must realize that the method determines only "free cortin." Much of it might be excreted in a combined form which escapes detection with Daughaday's method.

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APPENDIX

Determination of Corticosteroids

1. *Hydrolysis.* A specimen of urine collected over a twenty-four hour period is stored

in the ice box without preservative. Within twelve hours after the collection, a 300 ml. sample is withdrawn and the pH adjusted to 1.0 with concentrated sulfuric acid.

2. *Extraction.* Immediately thereafter, the contents are extracted twice in a separatory funnel with 2 to 75 ml. portions of chloroform. Centrifugation is employed for breaking the emulsion.
3. *Washing.* The combined chloroform extracts are washed first with 2 to 20 ml. portions of 0.1 N NaOH, then twice with distilled water, and dried with 1 to 2 Gm. of anhydrous Na_2SO_4. The solution is filtered through glass wool and evaporated to dryness under vacuum and at a temperature not exceeding 40°–50° C.
4. *Partition between benzene and water.* The residue is taken up in 2 ml. of benzene and transferred quantitatively to a separatory funnel by rinsing with three 1 ml. portions of benzene. The benzene extract is then partitioned four times with distilled water in amounts of one 10 ml., two 9 ml., and one 8 ml. portions, respectively. The benzene solution is then transferred quantitatively to a small flask and concentrated to dryness under vacuum and low temperature. The residue is dissolved in 0.2 ml. of glacial acetic acid. Distilled water is added to the solution to make a total of 9 ml.
5. *Oxidation.* To the 9 ml. of aqueous solution is added 0.5 ml. of periodic acid reagent, prepared by dissolving 0.69 Gm. of KIO_4 in 100 ml. of 0.5 N H_2SO_4. A blank consisting of 9 ml. of distilled water is run simultaneously. The oxidation is allowed to proceed at room temperature for forty-five minutes, after which the oxidation is stopped by the addition of 0.5 ml. of stannous chloride solution. The latter is prepared by dissolving 1.41 Gm. of $SnCl_2 \cdot 2H_2O$ in 50 ml. of 2.5 N HCl. The entire step is carried out in a small flask which can be attached to a distillation assembly.
6. *Distillation.* The distillation is effected with careful heating. The distillate is collected in a 15 ml. graduated centrifuge tube to which 1 ml. of distilled water has been added. The final volume is adjusted to 9 ml.
7. *Color formation.* To 5 ml. of the distillate in a large tube (200×20 cm.) is added 1 to 10 ml. of 10 per cent chromotropic (acid) solution and 5 ml. of concentrated H_2SO_4. The tubes are heated for thirty minutes in a boiling water bath, then cooled at 25° C. and the optical density determined in a Coleman spectrophotometer at a wave length of 570 m/m.

PREMENSTRUAL TENSION TREATED WITH VITAMIN A

JOAQUÍN ARGONZ, M.D. AND CARLOS ABINZANO, M.D.

From the Service of Endocrine Diseases of the Rivadavia Hospital, Buenos Aires, Argentina

THE purpose of this paper is to communicate the results obtained in the treatment of cases of premenstrual tension by means of large daily doses of vitamin A administered during the second half of the menstrual cycle.

The syndrome of premenstrual tension was described by Frank (1931 (1)) and its characteristic is the marked increase in the usual nervousness of the days immediately preceding menstruation. The syndrome manifests itself by subjective symptoms and somatic disorders of transitory, multiple and varied character. For convenience, they can be separated into three groups: 1) Symptoms referable to the nervous system, such as nervousness, emotional instability, insomnia, headache, psychic depression, physical asthenia, neuralgias, and fainting. 2) Tenderness of the abdomen and rapid increase in weight due to fluid retention, followed by a fall to the previous level immediately after menstruation. 3) Cyclomastopathies covering all the changes from simple painful distention of the breasts up to actual formation of nodules and glandular cysts. This syndrome, either full blown or partial, usually appears from seven to fourteen days previous to the onset of menstruation, vanishing the first or second day of the menstrual flow. At this moment, the characteristic symptoms of dysmenorrhea usually present themselves.

The great majority of the patients showing these symptoms, were greatly benefited by the new treatment, and the results obtained with it are far superior to those previously obtained by us with the different types of treatment commonly used.

CLINICAL MATERIAL AND METHODS

The patients were seen in the out-patient department, where they went to seek medical advice for their premenstrual symptoms. Although the total number of patients treated to date is much larger, this paper deals only with the results obtained in the first 30 patients, as the rest of them showed similar response to this therapy.

Table 1 summarizes the main features of the cases from the clinical point of view. The ages of the subjects varied between 17 and 47, most of them

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TABLE 1. SUMMARY OF DATA FROM 30 REPORTED CASES OF PREMENSTRUAL TENSION

Case No., age, and marital status	Mastodynia and adenosis	Cystic disease of the breast	Abdominal and pelvic pain	Edema	Nervous tension	Backache	Menstrual cycle	Cytology of the urinary sediment*
1 27—S.	++	–	++	++	+++	–	Oligomenorrhea Dysmenorrhea	Estrogenic
2 26—M.	++	–	+	++	+++	–	Hypomenorrhea Dysmenorrhea	Estrogenic
3 42—M.	++	–	–	+	+++	++	Hypomenorrhea	Estrogenic
4 27—S.	+++	–	++	++	–	–	Dysmenorrhea	Estrogenic
5 25—S.	+++	–	++	–	–	–	Normal	Estrogenic
6 26—S.	++	–	++	–	+	–	Hypomenorrhea Dysmenorrhea	Hypoestrogenic
7 26—S.	++	–	++	++	+	–	Dysmenorrhea	Estrogenic
8 35—M.	++	–	++	–	–	–	Dysmenorrhea	Estrogenic
9 40—S.	++	–	+++	++	+++	–	Dysmenorrhea	Hypoestrogenic
10 29—S.	++	–	++	–	+	–	Dysmenorrhea	Full estrogenic
11 47—M.	++	–	+	–	+	–	Dysmenorrhea	Full estrogenic
12 25—S.	++	–	+++	–	++	–	Dysmenorrhea	Estrogenic
13 24—S.	++	–	+	–	–	–	Oligomenorrhea Dysmenorrhea	Estrogenic
14 33—M.	+++	–	++	++	+++	++	Dysmenorrhea	Estrogenic
15 35—S.	++	–	–	++	++	–	Hypomenorrhea Dysmenorrhea	Estrogenic
16 32—M.	+++	–	++	++	++	–	Dysmenorrhea	Full estrogenic
17 43—M.	+++	–	++	++	+	++	Dysmenorrhea	Estrogenic
18 29—M.	++	–	–	++	++	–	Oligomenorrhea	Hypoestrogenic
19 33—M.	+++	–	–	–	+	–	Dysmenorrhea	Estrogenic

TABLE 1—*continued*

Case No., age, and marital status	Mastodynia and adenosis	Cystic disease of the breast	Abdominal and pelvic pain	Edema	Nervous tension	Backache	Menstrual cycle	Cytology of the urinary sediment*
20 31—S.	++	−	++	++	+	−	Dysmenorrhea	Full estrogenic
21 27—M.	+++	−	+++	+++	+	++	Dysmenorrhea	Estrogenic
22 22—S.	+++	+++	−	−	−	−	Dysmenorrhea	Estrogenic
23 24—S.	+++	++	−	−	++	++	Normal	Estrogenic
24 36—M.	+++	+++	−	−	++	−	Normal	Estrogenic
25 38—M.	+++	−	+++	++	++	+++	Oligomenorrhea Dysmenorrhea	Estrogenic
26 30—M.	+++	−	+++	−	++	+++	Dysmenorrhea	Estrogenic
27 17—S.	++	−	++	−	−	−	Dysmenorrhea	Hypoestrogenic
28 35—M.	+++	−	+++	−	−	+++	Dysmenorrhea	Hypoestrogenic
29 44—M.	++	+	−	−	+	−	Dysmenorrhea	Estrogenic
30 46—M.	+++	+++	++	+	+++	++	Normal	Estrogenic

* Del Castillo, Argonz, and Galli Mainini (2).

being between 25 and 35 years of age. Fourteen were unmarried and 16 married.

Mastitis was a constant symptom, being present in various degrees of severity in all patients. The majority of them had only cyclic painful distention due to hyperemia and edema of the interstitial tissue of the breasts. Others showed the characteristic features of adenosis or mazoplasia, that is to say, small and multiple nodules which gave a granular consistency to the mammary tissue. Five of these patients (Nos. 22, 23, 24, 29 and 30) had isolated large nodules of the type seen in cystic mastopathy.

Painful tension of the abdomen and tenderness in the pelvis followed mastodynia in frequency; 80 per cent of the patients complained of these symptoms. Some patients had vomiting or diarrhea, clinical signs which have been considered due to edema of the intestinal wall.

Fifty per cent of the patients showed edema of subcutaneous cellular tissue. This edema manifested itself chiefly in the legs. There was a rapid increase in weight during this premenstrual period, followed by a loss during menstruation.

Symptoms referable to the nervous system were detected in various degrees in 80 per cent of the patients. Some showed increased nervousness and emotional instability during this period; others complained of various types of headaches, some had insomnia, some paresthesias, or neuralgias of the lower limbs; and dizziness and fainting appeared in others. Backache of variable intensity was also reported by some patients.

Menstruation had normal characteristics in only 4 patients. Oligomenorrhea of from thirty-five to forty days' duration was present in 4 cases. The great majority—24 patients—had the typical picture of dysmenorrhea, which in some had the characteristic features of the so-called "expulsive" type.

Smears of the urinary sediment and the study of its cytologic content (2) as an index of estrogenic activity, were made in all the cases. Most of the smears showed a large quantity of cornified cells, varying from 40 to 80 per cent of the different types of cells found in the smears. This percentage, with the technique used, is higher than that found in normal women in comparable circumstances. Only 5 patients showed hypoestrogenic urinary smears.

The treatment of the patients with premenstrual tension, the results of which are communicated in this paper, consisted in the oral administration of 200,000 I.U. of vitamin A per day,[1] in two doses of 100,000 I.U. taken immediately after lunch and dinner respectively.

Because the symptoms usually present themselves during the two weeks before menstruation, we decided to begin the treatment on the fifteenth day of the cycle, using uninterruptedly the same daily doses up to the first day of menstruation, inclusively. Administration of vitamin A was then stopped and a new therapeutic course was started fifteen days later.

We had no previous personal experience and as far as we know, there was no other experience in the matter of doses, pharmaceutical form, route of administration and duration of such treatment in this syndrome. For this reason, we empirically indicated a treatment in our first patient and in view of the results obtained with it, we repeated the same treatment (just described) with the rest of the patients. We are not claiming that the doses we used are the best. Further experience might indicate that good

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[1] We are grateful to E. R. Squibb & Sons, Argentina S. A.; Abbott Laboratories, Argentina S.R.L.; and Spedrog Laboratories, for providing the therapeutic substance.

results can also be obtained with lower doses; or conversely, poor results may require larger doses.

The treatment has been well tolerated by all the patients. None of them complained of any discomfort, either systemic or referable to the gastrointestinal tract.

It is our experience with this new therapy, now over a year old, that in most cases it is necessary to repeat the treatment over a period of three or four months, in courses of fifteen days each, with daily doses of 200,000 I.U.

Some patients, who after several months of remission came back to us with attenuated symptoms of premenstrual tension, showed a good response with 100,000 I.U. daily.

RESULTS

The results obtained in the aforementioned first 30 patients, as in the ones treated later by ourselves and other colleagues, indicate the usefulness of the therapy and the obvious benefit that the patient derives from it.

Table 2 shows the changes in symptomatology which were observed. The beneficial effect of the therapy is apparent if Table 2 is compared with Table 1.

Placebos have been used in several patients in order to rule out the possibility of improvement by suggestion. When the placebo was administered during the first month, the symptoms of premenstrual tension appeared without variation; in some cases in which the vitamin A was replaced by the placebo in the second month of treatment, symptoms were present but in a milder form. A few patients who did not follow the recommended treatment, taking the vitamin A only for a few days or irregularly, did not react as favorably as the other patients did. When the indicated treatment was resumed by the patient, good results were obtained.

Painful tension of the breasts was a symptom common to all the patients, some of them having suffered from it for several years without getting any benefit from the various previous therapies administered.

In some of the patients who had had typical mastodynia, the picture progressively changed to the disorder known as adenosis or mazoplasia, characterized by the presence of small multiple nodules, which became very painful during the premenstrual period.

Mastodynia practically disappeared under treatment in 20 of the 30 patients, improved in 3, and was unaffected in 1 patient. The improvement was shown by the distention of the breasts and the marked reduction of pain, leaving only the usual dull tenderness felt by the normal woman.

TABLE 2. RESULTS OBTAINED IN PREMENSTRUAL TENSION BY THE USE OF VITAMIN A

Case number	Masto-dynia and adenosis	Cystic disease of the breast	Abdominal and pelvic pain	Edema	Nervous tension	Back-ache	Menstrual cycle	Cytology of the urinary sediment
1	0	−	0	0		−	Oligomenorrhea	Estrogenic
2	0	−	0	0	0	−	Normal	Estrogenic
3	++	−	−	+	++	+	Normal	Estrogenic
4	0	−	+	0	−	−	Dysmenorrhea	Estrogenic
5	0	−	0	−	−	−	Normal	Estrogenic
6	0	−	+	−	+	−	Dysmenorrhea	Estrogenic
7	0	−	0	0	+	−	Normal	Estrogenic
8	0	−	0	−	−	−	Normal	Estrogenic
9	0	−	+	0	+	−	Normal	Hypoestrogenic
10	0	−	+	−	0	−	Dysmenorrhea	Estrogenic
11	0	−	+	−	0	−	Oligomenorrhea; cycles, 47 and 50 days	Estrogenic
12	0	−	+	−	+	−	Normal	Estrogenic
13	+	−	0	−	−	−	Oligomenorrhea	Estrogenic
14	0	−	0	0	+	0	Dysmenorrhea	Estrogenic
15	0	−	−	0	+	−	Normal	Estrogenic
16	0	−	0	0	0	−	Normal	Estrogenic
17	0	−	0	0	0	+	Normal	Estrogenic
18	0	−	−	0	+	−	Normal	Estrogenic
19	0	−	−	−	0	−	Oligomenorrhea; cycle, 45 days	Estrogenic
20	+	−	0	0	0	−	Dysmenorrhea	Estrogenic
21	0	−	+	0	+	+	Dysmenorrhea	Estrogenic
22	0	0	−	−	−	−	Normal	Estrogenic
23	0	0	−	−	+	0	Normal	Estrogenic
24	0	+	−	−	+	−	Normal	Estrogenic
25	0	−	0	0	+	0	Normal	Estrogenic
26	+	−	+	−	0	+	Oligomenorrhea; cycle, 54 days	Estrogenic
27	0	−	++	−	−	−	Normal	Hypoestrogenic
28	0	−	0	−	−	0	Normal	Estrogenic
29	0	0	−	−	0	−	Dysmenorrhea	Estrogenic
30	0	+	+	0	+	0	Normal	Estrogenic

The majority of these results were obtained after the first month, the improvement increasing the second and third month.

When adenosis was present, the infiltration of the interstitial tissue disappeared in the first month although painful nodules persisted during this time and it was only after the second or third month that they diminished in size, until they finally disappeared entirely.

The most advanced clinical picture of the disease was exhibited by patients No. 22, 23, 24, 29 and 30, in whom isolated large cysts with greatly increased fibrosis were present. In 3 of these patients cysts disappeared under treatment for two to five months. In the remaining 2, marked improvement has been obtained up to this moment, as shown by the decrease in size and consistency of the cysts and the disappearance of the pain.

A remarkable example was Case No. 22, a young girl 22 years old, who since her menarche when 14 years old, suffered from painful distention of the breasts. This condition was complicated three years before by the appearance of two nodular cysts which remained unchanged in spite of adequate treatment with progesterone and testosterone propionate. In December 1948, treatment with 200,000 I.U. of vitamin A daily was instituted during the fifteen days preceding menstruation. In January the distention and pain were decreased but the cysts were still present. This symptomatology was unchanged the following month, but in March the mastodynia disappeared and a marked decrease in the size of the cysts was noted. In April the nodules hardly could be palpated and, having lost their previous consistency, it was difficult to differentiate their limits within the mammary tissue. Treatment was interrupted the following month and the patient did not complain until July, when she noted a slight mastodynia. The treatment was then reassumed and continued in a smaller daily dose, 100,000 I.U., with satisfactory results up to the present.

Of the 22 patients suffering pelvic and abdominal pains during the premenstrual period, 10 showed marked improvement and 12 were completely relieved even several months after the cessation of the therapy.

Edematous infiltration of the subcutaneous tissue, especially noticeable in the legs, was also favorably affected by the treatment. Fourteen out of 15 patients with this disorder were freed of it by the therapy and a marked reduction was noted in the other patient.

According to our own determinations, some of these patients who had an increase in weight up to 2 or 3 Kg. during the premenstrual period remained unchanged in their weights under vitamin A therapy. Coincidentally, we should point out that the majority of the patients had an increasing diuresis after a few days of treatment.

The bizarre symptoms which we have grouped under the denomination

of nervous tension, such as irritability, emotional instability, headaches, insomnia, dizziness, and cutaneous paresthesias, have also been favorably modified. They disappeared in 9 and markedly improved in 14 of the 23 patients who had had these symptoms. Patients with habitual headaches which were aggravated during the premenstrual period were not brought under control with the medication. Back pain was improved in most of the patients.

As mentioned previously, the menstrual cycle was altered in the majority of the patients. Following the therapy, dysmenorrhea practically disappeared in 17 patients and markedly improved in the remaining 7.

We have observed in Cases No. 11, 19 and 26, a lengthening of the menstrual cycles, which in one instance was postponed up to fifty-four days. This phenomenon took place again in some later patients, thus establishing a remarkably interesting point. In this respect, we should like to mention Fasold (3) who, treating young girls with endemic goiter with vitamin A, observed that oligomenorrhea and amenorrhea were produced in some of the patients, with improvement of these conditions after the cessation of the vitamin A administration.

We were specially interested in the study of the menstrual cycle as shown by the cytologic content of the urinary sediment and the vaginal smear. As we have already stated, we found normal estrogenic smears in the majority of the patients, but with a higher percentage of cornified cells. Hypoestrogenic smears were found in only 5 patients, in 3 of whom there was reversion to estrogenic patterns under vitamin A administration. No change was observed in the remaining 2. With this exception, up to the present we have been unable to detect any noticeable variation of the type or percentage of cells after completion of the treatment, indicating that the urethra and vagina did not modify their type of desquamation under the instituted therapy.

DISCUSSION

These clinical observations and the results obtained with this new therapy call for an explanation of the mode of action of vitamin A in the treatment of premenstrual tension. Unfortunately, we are not in a position to make such a statement because of the lack of conclusive clinical facts or experimental proof. We only dare to advance an hypothesis based on the present knowledge of the action of vitamin A on the neuro-endocrine mechanism which controls the menstrual cycle in the woman.

Frank (1) attributes the syndrome of premenstrual tension to an excess of circulating estrogen, which in turn would be due to an elevation of the renal threshold. Most observers agree with the first part of his statement,

but not with the second. Thus, Greenhill and Freed (4) suggest that hyperestrogenism produces sodium retention, which is responsible for the edema, including the nervous system, from which the syndrome originally manifests itself. Israel (5) instead, attributes the syndrome to a deficiency of progesterone; and conversely, Gillman (6) suggests that these cases show an excess of circulating progesterone.

Another more recent theory has been put forward by Salmon (7) who considers emotional trauma as the cause of the increased production of estrogens, or an increase of the organic sensitivity to normal quantities of this hormone.

Certain cases of premenstrual tension, according to Zondek (8), represent an allergic phenomenon of endocrine origin; and recently Taylor (9) brought up to date the publications of French authors who consider that most of these symptoms are due to pelvic hyperemia and congestion.

In relation to these different hypotheses, we may say that the great majority of our patients had hyperestrogenic urinary and vaginal smears, which would be in accordance with Frank's point of view. Nevertheless, it should be kept in mind that in our patients, in spite of the clinical improvement obtained with the treatment, the smears did not show any important change, the percentage of cornified cells being the same before and after the treatment. About this point, it can also be argued that the degree of response is different for the urethra and vagina on one hand, and the rest of the affected organs, on the other.

In relation to the theory which maintains that premenstrual tension is due to sodium retention, it is interesting to recall that in a number of our patients, an increased diuresis took place under vitamin A therapy. This effect has already been shown by Bicknell and Prescott (10) in patients receiving 144,000 I.U. daily of vitamin A throughout several weeks.

We know only one clinical antecedent in relation to the therapeutic action of vitamin A and that is Simkins' (11) patient, who had hyperthyroidism which showed an accentuation of the nervous disorders during the premenstrual period and after treatment with high doses of vitamin A showed a marked improvement.

The response of our patients to vitamin A might suggest that they suffered from hypovitaminosis, but we were not able to find signs of deficiency in any of them. We do not consider as such the occasional discrete follicular hyperkeratosis observed in some cases. Moreover, hypovitaminosis is very rare in countries such as ours, where the common diet is rich in vitamin A.

If, in order to explain the mode of action of vitamin A in premenstrual tension, we search the literature of experimental medicine or biology, we

find really very few works on its influence on the organs related to the menstrual cycle; and furthermore, unfortunately, results are extremely contradictory.

Concerning the pituitary gland, Mason and Wolfe (12) claim that vitamin A deficiency increases gonadotropic potency in the rat. Sutton (13), feeding a young bull with a vitamin A deficient diet, reached the same conclusion. On the other hand, Van Os (14) in experiments with rats fed a diet deficient in vitamin A, found a reduction of the pituitary gonadotropins.

In relation to the ovary, Truscot (15) showed that there was an increase in number and in size of the follicles in rats receiving vitamin A; however, Brody (16) did not find any change after injecting 10,000 to 40,000 I.U. of vitamin A; and De Venanzi (16) observed, after injecting large doses of this vitamin, changes in the estrus and an increase in the number of corpora lutea.

It is obvious that the results of these experiments are insufficient to explain the action of vitamin A in premenstrual tension as an effect of this vitamin upon the pituitary gland or the ovary.

Concerning the mastodynia, which improved in such striking and constant manner under vitamin A therapy, we must remember that this symptom is considered to be due to hyperplasia of the connective and glandular tissue and to interstitial edema present during the days preceding menstruation. The first phenomenon, that is to say, the hyperplasia and hyperemia, must be related to hormonal action, presumably estrogenic. This effect would be more marked in these cases, either because of an excess production of estrogen caused by an anomaly of its metabolism and excretion, or else because of a target organ predisposed to react with greater intensity to the physiologic action of this hormone. At this point it is interesting to mention the work of Studer (18) who has proved that the abnormal hyperplasia and hyperemia of the thyroids of mice under the administration of thiouracil, is counteracted if vitamin A is administered at the same time. This substance would have a protective action which would impede the tissue modification provoked by hormonal factors in such circumstances.

Without being able to offer any sound experimental or clinical proof, we set forth the hypothesis that vitamin A acts by modifying a disorder in the metabolism of estrogens.

The present knowledge of the matter, even if incomplete and subject to a great deal of adjustment, permits the conclusion that certain enzymes of the "estrinase" type found in some tissues and especially in the liver, are related to the metabolism of estrogens. The disturbance of this enzymatic process would result in an increase in the circulating inactivated

estrogens, which would then be the cause of the syndrome of premenstrual tension. The action of vitamin A on the liver would regulate the altered metabolism in an unknown manner, modifying favorably the manifestations of the syndrome.

SUMMARY

Thirty patients suffering from premenstrual tension are presented, their chief complaints being mastodynia, tenderness of the abdomen, edema and disorders of the nervous system.

These patients received 200,000 I.U. of vitamin A orally per day, during the second half of the menstrual cycle. Treatment was stopped at the onset of menstruation and resumed two weeks later, repeating the same course from two to six months.

Considerable improvement was obtained in the majority of patients by means of this therapy, as shown by the disappearance of mastodynia, decrease or disappearance of mammary nodules, marked decrease of abdominal pain, disappearance of edema and great improvement in the nervous disorders. This improvement continued after cessation of the therapy and the disturbing symptoms did not reappear during the year following the beginning of treatment. In this manner, the authors (19) have confirmed results obtained and published in a previous paper.

Results have not been as successful in patients who received vitamin A irregularly or only for short periods of time. On administering placebos, the symptoms remained unchanged.

This new treatment raises the question of the action of vitamin A on the pituitary-gonadal mechanism, as some of the patients showed deviations in duration and character of their menstrual cycle while under medication.

An hypothesis explaining the effects produced by the vitamin A is put forward, without offering a sound explanation of the mode of action of this new therapy because of the scarce and contradictory nature of the experimental work dealing with relationships between vitamin A and the pituitary and gonads.

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EFFECT OF PITUITARY ADRENOCORTICOTROPIC HORMONE (ACTH) IN A CASE OF PEMPHIGUS FOLIACEUS*

F. HOMBURGER, M.D., C. D. BONNER,† M.D.
AND W. H. FISHMAN, PH.D.

From the Clinical Research Laboratory of the Jewish Memorial Hospital, Roxbury, and the Departments of Medicine and Biochemistry, Tufts College Medical School, Boston, Massachusetts

PEMPHIGUS foliaceus is a chronic skin disease of young adults, with a mortality rate of about 40 per cent (1). It is a severely incapacitating disorder of unknown etiology and poorly understood pathogenesis. Among its peculiarities are the prevalence of Jewish people amongst those so affected and the tendency of these patients to high eosinophil counts. In the light of recent knowledge on hematopoietic effects of hormones of the adrenal cortex, this latter fact would attract attention to the adrenal cortex as a factor in the pathogenesis of this disease. Previous observations have suggested that the adrenal might play such a role in various types of pemphigus. Talbott, Lever and Consolazio (2) studied metabolic changes in 34 patients with pemphigus and found that patients "with acute pemphigus showed many changes in the serum which suggest adrenal insufficiency." They also found pathologic evidence that "damage to the adrenal glands was associated with the pathogenesis of the blood studies." The literature on the adrenal cortical pathology in pemphigus has been reviewed by Goldzieher (3), who reported 6 cases of his own and added a seventh in 1946 (4). His observations were "compatible with the view that function of the adrenal is impaired in persons with pemphigus." The evidence to this effect has so far been indirect and inconclusive. Lever and Talbott in 1944 (5), following an additional metabolic study on 17 cases, stated that "no etiologic significance can be attached to the chemical changes. They are regarded as a secondary symptom produced by the disease."

Since it is believed that ACTH as prepared to-day is a reasonably specific agent for the stimulation of the adrenal cortex, it may be reasoned that clinical or biochemical changes observed in a patient with pemphigus

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The ACTH used in this study was purchased with funds of the National Institute of Health from the Armour Laboratories, Chicago, and some ACTH was also donated by the Searle Co., Chicago.

† Damon Runyon Research Fellow.

receiving ACTH could be attributed to the patient's adrenal gland responding to such stimulation. One possible interpretation of such observations might be that adrenal hormones may play a role in this skin disease.

METHODS

A patient with pemphigus foliaceus (*see* case history) was given repeated courses of ACTH and her 17-ketosteroid excretion, sedimentation rate of red blood cells, circulating eosinophil levels, serum β-glucuronidase and electrophoretic patterns of blood plasma were followed and the findings correlated with the extent and severity of the skin lesions. The laboratory methods used were the following:

17-Ketosteroids were determined by the modified method of Talbot *et al.* (6).

Sedimentation rate of red blood cells was measured by the Wintrobe method.

Circulating eosinophils: 400 white cells were counted on smears obtained from venous blood and the circulating eosinophils were calculated from these data and the number of white cells.

The β-glucuronidase was measured by the method of Fishman *et al.* (7).

Electrophoresis was carried out in a citrate buffer of 0.01 ionic strength at pH 6.8.

The clinical course was recorded by 35 mm. Kodachrome photographs.

RESULTS

The observations are recorded in Chart 1 and in the accompanying photographs.[1] The following points may be particularly emphasized:

The excretion of 17-ketosteroids in this patient was not particularly low initially but there was no marked response until the fifteenth week of observation. This coincided with the most marked drop of the sedimentation rate and the most striking clinical improvement. In spite of the failure of the 17-ketosteroids to increase markedly, the eosinophils were wiped out three times before by daily doses of 75 mg. and 100 mg. of ACTH. On each occasion this eosinophil response was accompanied by varying degrees of clinical improvement. There were relapses whenever the dose of ACTH was lowered, and the eosinophil levels rose. The γ globulin decreased following a course of some seven weeks of 100 mg. daily of ACTH and returned to normal with remarkable rapidity once ACTH was discontinued. In view of observations on changes of the β-glucuronidase in

[1] The clinical severity of the skin lesions referred to in Chart 1 was evaluated and graded by means of photographs taken at intervals indicated in the bottom line of the abscissa (Figs. 1 through 11).

patients with other diseases, who received ACTH (Homburger *et al.*, unpublished observations), it is of interest to note that in this case there was no clear-cut correlation between the serum activity of this enzyme and the administration of ACTH or the clinical course.

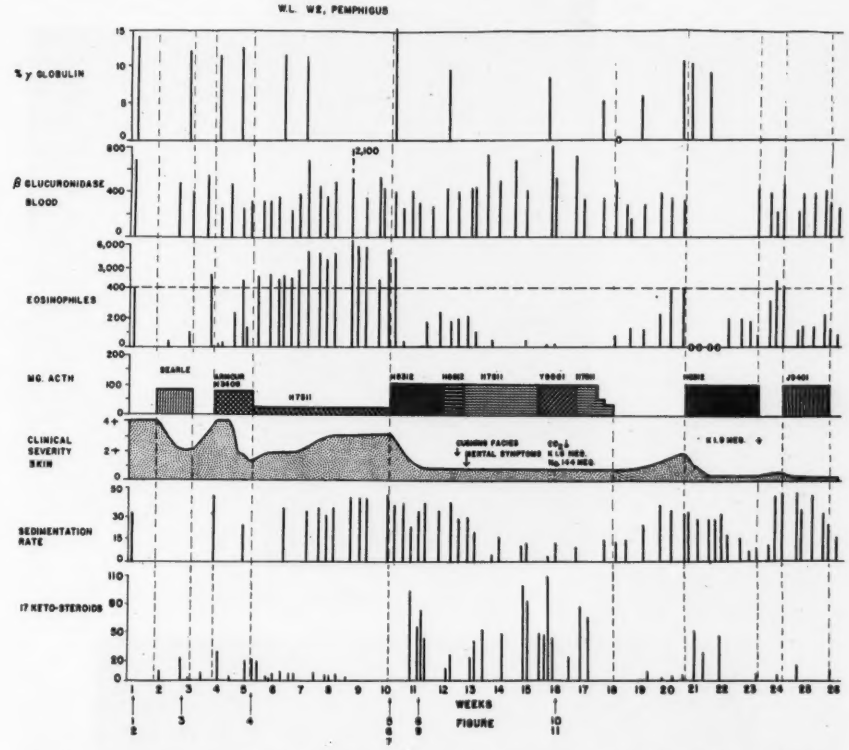

Chart 1. Summary of biochemical and clinical observations carried out in Patient L., beginning Nov. 3, 1949. This figure is self-explanatory. Comments are found in the text. The potency of the ACTH is expressed in mg. of Armour's standard. The varying degrees of severity of the skin lesions are illustrated in Figures 1–11.

DISCUSSION

The distinction between the various clinical types of pemphigus is often difficult and based exclusively on clinical observations. It is possible that the studies made in this case of classic pemphigus foliaceus may apply to other forms as well. The adrenal pathology has so far been investigated for the most part in pemphigus vulgaris (3, 4).

The data published in this paper demonstrate that remissions of this skin disease followed the administration of appropriate doses of ACTH

FIG. 1. Nov. 6, 1949. Extensive lesions of pemphigus foliaceus before treatment.

FIG. 2. Close-up of dorsal lesions, Nov. 6, 1949, before treatment.

and that relapses occurred rapidly whenever the medication was discontinued. The clinical remission paralleled changes of the circulating eosinophil levels, of the sedimentation rate and, to a lesser extent, the γ globulin levels. There was only a moderate increase in the 17-ketosteroid

FIG. 3

FIG. 4

FIG. 3. Nov. 18, 1949. Close-up of dorsal lesions following treatment with 200 mg. of Searle ACTH for ten days, equivalent to 80 mg. of the Armour standard per day. Considerable improvement is noticeable.

FIG. 4. Dec. 4, 1949, at the end of ten days of treatment with 100 mg. Armour standard ACTH per day. Notice cleared areas in lumbar region, buttocks, forearm and back.

excretion until late during therapy and after repeated remissions had been induced. Towards the end of this study the clinical remission persisted, as long as ACTH was given, even though ACTH did not cause a new increase of 17-ketosteroids. It is also of interest that a Searle prepara-

tion of ACTH, used first, caused only a slight increase of 17-ketosteroid excretion but a marked reduction of the eosinophils and clinical dermatologic improvement. It is impossible to know whether the failure of the Armour preparation H3406, used next, to increase urinary 17-ketosteroid

FIG. 5. Jan. 7, 1950, after reduction of daily dosage to 20 mg. per day for thirty-four days. Recurrence throughout tegument, particularly marked on thighs.

levels was due to a property of this lot or whether the prolonged administration of low doses of ACTH from the fifth to the tenth week may have primed the adrenal for the huge 17-ketosteroid excretions that followed large doses at the end of this pretreatment. Simultaneously with this marked 17-ketosteroid excretion, the toxic symptoms of alkalosis and hypokaliemia appeared. There was no absolute correlation between 17-ketosteroid levels and clinical improvement, inasmuch as the remissions persisted during ACTH therapy, in spite of low 17-ketosteroid levels. The interpretation of these observations must await further study.

SUMMARY AND CONCLUSION

A patient with pemphigus foliaceus is presented, in whom remissions were induced repeatedly by ACTH and were repeatedly followed by relapses upon withdrawal of the hormone. These observations are consistent with earlier evidence pointing to the possibility that the adrenal cortex may play a role in this skin disease.

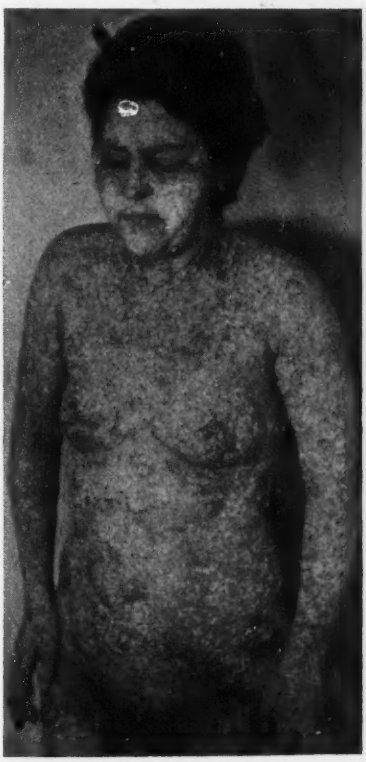

FIG. 6. Jan. 7, 1950, showing generalized pemphigus foliaceus.

Case History

W. L. was a 50-year-old white married female, who entered the Jewish Memorial Hospital on November 2, 1949, with a three years and nine months' history of skin disease. Her first medical record was in May, 1946, commencing on her admission to another hospital, where she was seen by a staff of dermatologists and internists and a diagnosis of pemphigus foliaceus was made. At that time she had a three months' history of bullous, weeping, crusting lesions which covered her body, and she entered the hospital because of prostration and a temperature indicative of sepsis. The lesions had first begun

on her back, under her breasts, on her abdomen, face, scalp and lower extremities, and finally appeared on the arms and hands. She was treated with penicillin, acetarsone, stilbestrol and 400 units of filtered x-ray to the spleen.

She was discharged in November, 1946, with her body still covered with dry crusts, and only a few areas of normal skin on her arms. The laboratory data were not remarkable at that time. She was followed by private doctors until September, 1947, with no improvement. She had gradually lost weight and was becoming bed-ridden. At this time she was seen by other dermatologists, who concurred with the diagnosis previously made. In addition to the large, greasy, moist, undermined scales on her body, there was a

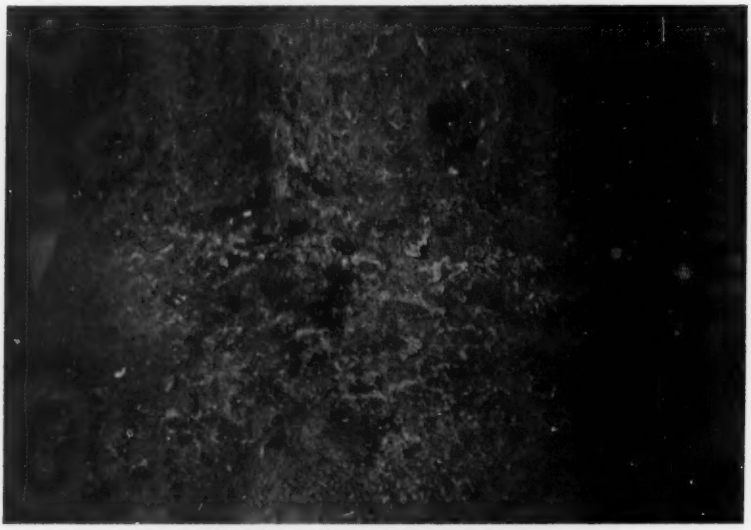

FIG. 7. Jan. 7, 1950. Compare this close-up of lumbar region with Figure 4. Notice severity of recurrence.

peculiarly disagreeable odor. At this hospital she received x-ray treatment, a total of 900 R to her liver and spleen, a high protein diet, high vitamin dosage, daily potassium permanganate baths, and topical ointment therapy for body and scalp. She improved slightly, and was discharged after 109 days in the hospital to continue the same treatment at home. Her skin was still in a diseased condition.

The patient also had a one-day admission to the Pratt Diagnostic Hospital, and dermatologic consultation again resulted in a diagnosis of pemphigus foliaceus. The same suggestions were made concerning therapy, and boric baths, bran baths, soda baths, and oatmeal baths were also added to the regime. Again she carried on at home under the care of a private physician, until October, 1949, when she entered still another Boston hospital, with her whole body covered with white, flaky scales. These could be easily scraped off and left red, oozing, denuded areas. There was a musty odor to the lesions. She was again seen by other dermatologists. A diagnosis of pemphigus foliaceus was again made and she was transferred to the Jewish Memorial Hospital for further treatment.

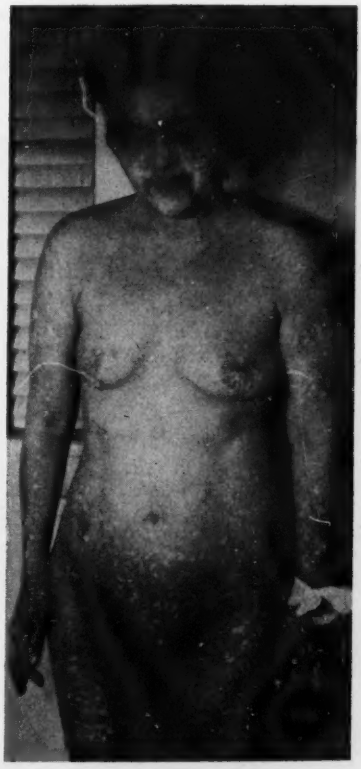

FIG. 8. Jan. 13, 1950, after six days of treatment with 100 mg. per day of Armour ACTH. Notice rapidity of remission on trunk (compare with Fig. 6) and relatively slower regression on thighs.

FIG. 9. Jan. 13, 1950. Close-up of nearly complete regression of dorsal skin lesions.

↓

On admission to this hospital, her past history was found to be unremarkable except for that dealing with the present illness. There was nothing unusual in the family or the social history; menstrual history revealed that her menarche occurred at 13 years of age, and irregular periods at intervals of from twenty-six to thirty days; the menopause

FIG. 10

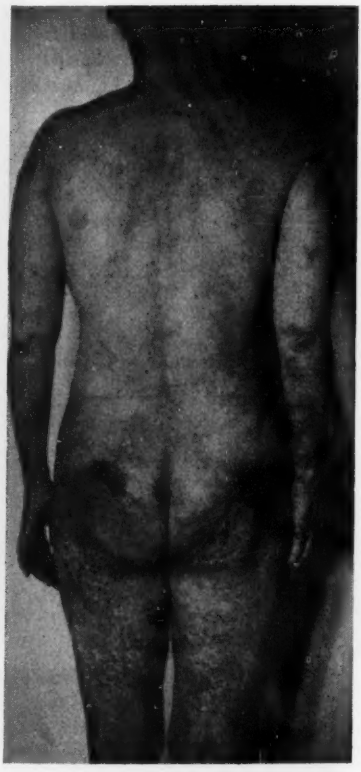

FIG. 11

FIG. 10. Feb. 20, 1950. After forty-four days of treatment with 100 mg. ACTH Armour standard per day. Notice completeness of remission, Cushing's type facies with hirsutism, and darker pigmentation of facies and areolae.

FIG. 11. Posterior view, taken on same day as Figure 10.
Notice scars from abscesses on left buttock.

occurred at the age of 47, and there had been no uterine bleeding since then. *Physical examination* revealed a well developed, fairly well nourished white female lying in bed in moderate distress. It was very difficult for her to move because of stiffness of muscles and tautness of skin. T. 98.4, P. 76, R. 20, B.P. 128/80. *Skin:* save for the tips of the fingers and the palmar areas of the feet, the entire surface of her body consisted

of pathologic skin. There were many white, flaky crusts, alternating with areas which were red and denuded; in other regions there was a serous type of exudate. Her scalp was involved, and the hair was matted. There was a disagreeable, strong odor which pervaded the whole room. There were no lesions in her mouth. The rest of the physical examination did not show anything abnormal.

Laboratory data revealed: *Urine*—pH 5.0, Sp.Gr.1.035, sugar 0, alb. 1−, acetone 0, bile 0, WBC 20–30, RBC 2–4, epith. cells; *Hematology*—Hgb.12.5 Gm., RBC 4.46 million, hematocrit 45 per cent, WBC 6,200, differential (poly. 58, lymph. 31, eos. 9, icterus index 1, sed. rate 35.5, buffy coat .5, mono. 2); *Blood chemistry:* NPN 34 mg./100 ml., tot. protein 7.5 Gm./100 ml., fasting blood sugar 87 mg./100 ml., calcium 10.4 mg./100 ml., phosphorus 4.2 mg./100 ml., alk.phosphatase .84 Bodansky units, chloride 71.6 mEq./L, sodium 143 mEq./L, potassium 2.3 mEq./L, and uric acid 6.8 mg./100 ml.

After completing preliminary studies, the administration of ACTH was started.

The subsequent course of the disease is discussed in the preceding sections of this paper and illustrated in Chart 1 and Figures 1–11.

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HYPOTHALAMIC LESION CAUSED BY BOECK'S SARCOID

Å. GJERSØE, M.D. AND K. KJERULF-JENSEN, M.D.
From the Medical Department, the Blegdams Hospital, Copenhagen, Denmark

NUMEROUS anatomic and physiologic studies during the last few years have shown the hypothalamus to be a center which co-ordinates the processes upon which the physiologic balance of the whole body depends, *e.g.*, regulation of body temperature, the metabolism of water, and to some extent the metabolism of fat, protein, carbohydrate, and minerals. Further, the hypothalamus controls the autonomic nervous system—the sympathetic as well as the parasympathetic. It controls sleep, several endocrine functions, and the more basal emotional reactions.

The regulating influence of the hypothalamus depends on an interplay of a stimulating and an inhibitory activity, which may proceed from the anterior and the posterior nuclei respectively. These contrasting actions are usually so well balanced that no single action is definitely noticeable. The close correlation between the hypothalamus and various secretory organs is partly of a nervous and partly of a humoral nature. Possibly also hormone-producing cells may be found in the hypothalamus. On histologic examination, cell nests situated in the supraoptic nucleus and in the paraventricular nucleus show accumulation of colloid substance and vacuolation. They are very richly vascularized and present an intense phosphate exchange. However, we know nothing further as yet of the nature of these hormones, if present. Perhaps it is these cells which act as chemosensible end organs.

We may conclude on the basis of physiologic and clinical observations in normal subjects that the hypothalamus plays a part in the control of oxygen intake, temperature regulation, water metabolism, the regulation of thirst, the metabolism of salt, carbohydrate, fat and protein, the regulation of appetite, cardiovascular and gastro-intestinal activities, respiration, sleep, sexual function, and emotional reactions (1) (2). Hypothalamic lesions may cause one or more symptoms corresponding to these—and possibly other—single functions. The symptoms are most often grouped in characteristic syndromes, *e.g.*, the nephrotic syndrome and diabetes insipidus. These are frequently dominated by the close correlation between the hypothalamus and the pituitary body (3).

Some clinical observations bear out the results of numerous experimental investigations. The case here reported affords an excellent example of signs and symptoms brought about by a hypothalamic lesion.

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CASE REPORT

A blind mechanic, aged 29, (Case No. 842/1948) had at the age of 17 been admitted to the Eye Department of the Rigshospital (State Hospital) with a supposed tuberculous iridocyclitis. X-ray examination of the lungs had shown glandular swelling paratracheally and in both hili with perihilar infiltrations. Owing to the progressive course, the left eye was enucleated in 1937 and the right in 1941. Microscopy of the left eye showed large and small circumscribed accumulations of epitheloid cells surrounded by a scanty round-cell infiltration all over the eye, but particularly in the iris, ciliary body, optic disk, and end of optic nerve. A few of the epitheloid cell nests also contained small "giant cells." *Histologic diagnosis:* Boeck's sarcoid.

The patient was well until the age of 27 (1946). From the end of 1946—*i.e.* eighteen

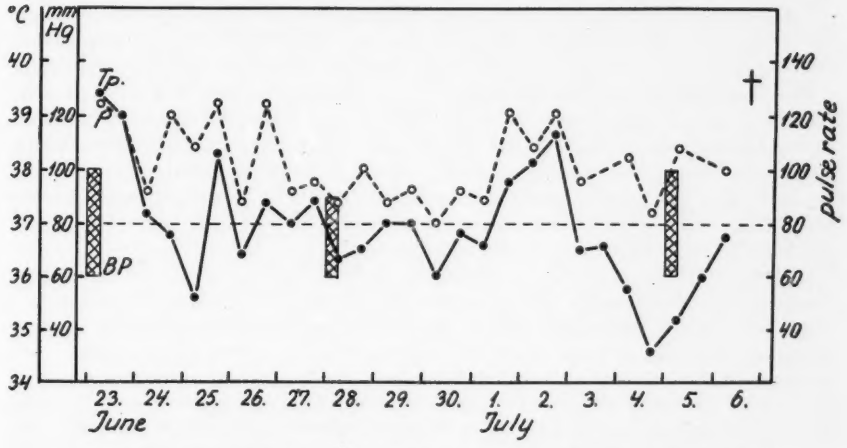

FIG. 1. Blood pressure, pulse rate and rectal temperature during the last fourteen days of the patient's life.

months before his admission—progressive mental changes were noticed. The patient grew fretful, irascible, unkind, listless, apathetic, and inert. The last few months before his admission he had been suffering from excessive sleepiness. In the course of 1947, moreover, increasingly frequent periods of dyspnea of the asthmatic type were noted; and the last six months before his admission he suffered from polydipsia, polyuria, and a tendency to feel cold.

State on admission, June 23 1948: The patient showed normal body development, nutrition, and distribution of subcutaneous fat. He was pale and highly febrile (39.4° C. = 103.3° F.) with severe dyspnea of the asthmatic type. His skin was dry and scaly. Body hair was scanty, and the external genitalia were hypoplastic. The lungs showed signs of bronchial asthma and right bronchial pneumonia. Otherwise the physical examination revealed nothing abnormal. Mentally the patient was very peculiar: euphoric, obtuse, apathetic with slow cerebration and pronounced sleepiness.

Course of illness: The patient was treated for his pneumonia with sulphathiazole and penicillin, and further with ephedrine, solution of thiophylamine, and phenobarbitone. During this treatment his temperature fell almost critically to subnormal values, but the temperature curve on the whole ran a strange course.

The pulse rates did not always parallel the temperature values. The dyspnea was not improved by the treatment. The blood pressure was low, the lowest value being 90/60 and the highest, 100/60 mm. of mercury.

The patient showed general edema, was always thirsty, drank up to 6½ liters a day, and had a correspondingly high diuresis. The specific gravity of the urine was low, never over 1003, even with normal urinary volumes. Finally a slight hemorrhagic diathesis developed. The mental changes grew more pronounced, and the initial excessive sleepiness was superseded by insomnia.

Laboratory examinations: Results of a Mantoux I test were negative and no tubercle bacilli were found in the sputum on microscopic examination or by culture. Roentgenograms: the lungs showed patchy shadowing of both basal fields, especially the right, which also presented a minor exudation. The skull showed nothing abnormal and, in particular, the sella turcica was normal. Electrocardiogram: paroxysmal auricular flutter and extra systoles. Blood—sedimentation rate, 30–47–119 mm./hr.; hemoglobin, 85-77-63 per cent; erythrocyte count, 3.60–2.73 million; leucocyte count, 11,200–7,200, with normal distribution; thrombocytes, 124,000. Plasma—sodium, 317 mg. per cent; total base 149 mEq./L. Serum—chloride, 386-366 mg. per cent; CO_2 combining power, 80-79 vols. per cent; cholesterol, 184 mg. per cent; calcium, 10.2 mg. per cent. Fasting blood sugar, 79 mg. per cent; blood urea, 16–25 mg. per cent; and total protein 6.7 Gm. per cent, with relative diminution of the albumin fraction (2.0) and increased globulin (4.7). Urine microscopy showed nothing abnormal and there was no proteinuria or glycosuria. The Wasserman reaction was negative.

Diagnosis: The patient died fourteen days after his admission, without an exact diagnosis having been made, but the tentative diagnosis was: hypothalamic lesion.

Autopsy: Along the trachea and in the posterior mediastinum there were pseudomelanotic, firm glands, larger than nuts, more or less like tumor conglomerates, with caseification. The lungs were large and edematous. In the right lung there was fibrinous pneumonia. In the left, there was a primary focus which was caseously and fibrously encapsuled, and a nut-sized cavity. There were no tubercles in the lungs, but there were caseous, fibrous changes with pseudomelanosis in numerous glands. The skull was normal and the sella turcica was not enlarged. The pituitary body was small. The brain was of normal shape and there was no tumor or hemorrhage in the hypothalamic area.

Histologic examination (by Bj. Vimtrup): In the cerebral tissue from the hypothalamic area, there was chronic inflammation with thick-walled vessels associated with abundant collagenic connective tissue with many fibroblasts and lymphocytes. In the connective tissue there were nests of larger cells with weakly staining, often net-like cytoplasm and a large succulent nucleus, many of which were of the character of epithelioid cells. There were numerous typical giant cells with peripheral nuclei; these were highly reminiscent of sections of Langhans' cells. Tubercle bacilli (acid-alcohol-fast rods) were not demonstrable. Histologic diagnosis: *Boeck's sarcoid* (Fig. 2).

DISCUSSION

The case here reported presents a hypothalamic syndrome caused by a destructive process, presumably Boeck's sarcoid. The signs and symptoms were as follows: 1) mental changes within the fields of intellect, will and emotion, 2) excessive sleepiness, later superseded by insomnia, 3) diabetes insipidus with polyuria, excessive thirst, salt (sodium chloride) retention, water retention (edema), and hypoalbuminemia without proteinuria, 4)

abnormal pulse variations, paroxysmal auricular flutter and pallor, 5) impaired capillary resistance, 6) hyperthermia-hypothermia, 7) hypopituitarism, and 8) (?) bronchial asthma.

The signs and symptoms just mentioned may be referred to the hypothalamus. One of the most striking features of the clinical picture is the fact that change of character, unprovoked emotional outbursts, and possibly bronchial asthma may be a preliminary to a syndrome of hypothalamic origin.

In the present case the disease must be supposed to have started as

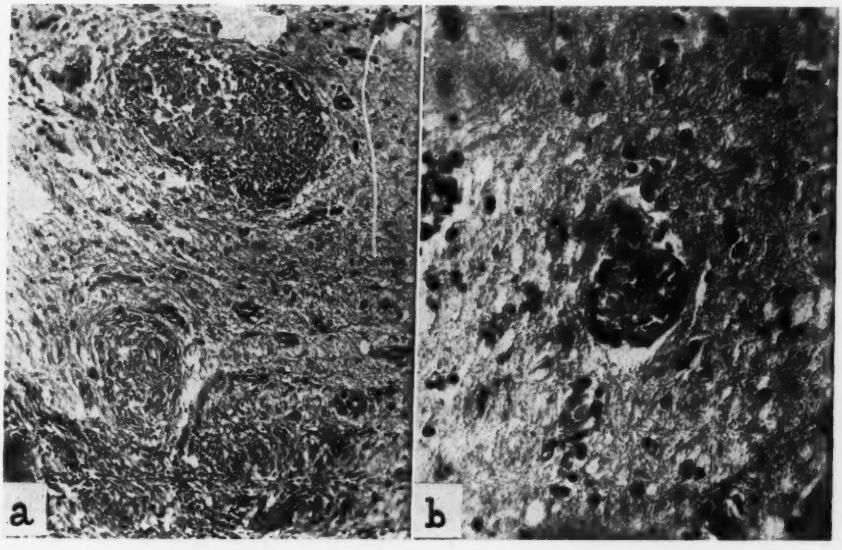

FIG. 2. *a* and *b*. L.P. and H.P. views respectively, of epithelioid granulomas of the hypothalamic area.

Boeck's iridocyclitis. The eye lesion has been described already by Schaumann (4), and before him by Heerfordt (5) as part of the syndrome of uveoparotid fever, which is now regarded as a manifestation of Boeck's sarcoid (6, 7, 8). Østerberg (9) in his compilation estimated the incidence of iritis in Boeck's sarcoid at 5 to 10 per cent. He pointed out the relatively good prognosis compared with that for tuberculous iridocyclitis. The latter is, moreover, more painful and less proliferative. Our case was thus in several respects highly reminiscent of tuberculous iridocyclitis. Biopsy is required in order to make the exact diagnosis. Jensen (10) mentioned various forms of the eye lesion: 1) Boeck's uveitis in uveoparotid fever, 2) iritis (nodular form), and 3) iridocyclitis, serous form with precipitates

behind the cornea. Our case seems to have been one of Boeck's iridochoroiditis with a lesion of the optic nerve as well. Similar cases have been described as "posterior uveitis" (11, 12).

It is strange that twelve years should elapse between the onset of the eye symptoms and the occurrence of the neurologic signs and symptoms. Cerebral manifestations are generally rare in Boeck's sarcoid. Gravesen (13) found such in only 1 out of 112 cases, and Nielsen (14) observed them in 4 out of 18 cases. A case with reflex abnormalities and a case with meningitis-like symptoms have previously been described (15, 16). In these cases postmortem examination revealed changes in the cerebral tissue or the meninges. Other cases with no histologic examination of the cerebral tissue are recorded and have been collected by Roos (17).

There are various instances of diabetes insipidus associated with Boeck's sarcoid. This must be due to changes in the pituitary body or the hypothalamus, or both. Heerfordt in 1909 described transitory diabetes insipidus during uveoparotid fever. Other writers have since described similar cases of diabetes insipidus in Boeck's sarcoid with epitheloid-cell granulomas in the pituitary body (18, 19). One case with radiographically verified changes of the sella turcica was of two years' duration (20).

Jersild (21) has described a 15-year-old boy with diabetes insipidus associated with a clinically well characterized Boeck's sarcoid. A follow-up examination carried out two years later by Gravesen (13), confirmed the benign course, as has also been observed by other writers (21, 22, 23).

In 1 patient with diabetes insipidus, described by Longcope (24), the pituitary and the hypothalamic tissue were transformed throughout to that characteristic of Boeck's sarcoid. Another patient with myxedema, polyuria, and later thrombopenia, described by Kraus (25), had granulomas in the infundibulum and the pituitary body. Panhypopituitarism was found in a patient with typical granulomas in the posterior pituitary lobe (26).

A hypothalamic involvement as shown by autopsy and histologic examination has thus been reported only in few cases (15, 24, 25, 27, 28, 29) in addition to the present case. It must be borne in mind, that the case here described did not present visible changes in the cerebral tissue, but marked histologic changes of the hypothalamic area. There is much evidence to suggest that Boeck's sarcoid affects chiefly the parts of the cerebrum with a high metabolic rate (the hypothalamus). This possibility should always be considered in cases of diabetes insipidus of unknown cause.

SUMMARY

A case is reported of a young man in whom, twelve years after the onset of Boeck's choroiditis, there developed mental and emotional disturbances,

slight hypogonadism, excessive sleepiness, asthma, auricular flutter, diabetes insipidus and hyperthermia alternating with hypothermia. Autopsy revealed Boeck's sarcoid in the hypothalamic area, but not in the pituitary.

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PSEUDOHYPOPARATHYROIDISM WITH DECREASED GLUCOSE TOLERANCE: REPORT OF A CASE*

ROBERT C. MOEHLIG, M.D. AND ROBERT A. GERISCH, M.D.

From the Department of Medicine and Department of Clinical Investigation, Harper Hospital, Detroit, Michigan

CASES of pseudohypoparathyroidism are rare. Albright and associates (1) first reported 3 cases from the Massachusetts General Hospital and 6 additional cases have been reported since then (2, 3, 4, 5, and 6). Albright states that pseudohypoparathyroidism has essentially the same symptomatology, chemical findings, and physical signs as hypoparathyroidism; however, the cause of the disturbance is not a lack of parathyroid hormone but an inability to respond to it. The syndrome has, in addition, certain developmental abnormalities which serve to delineate it from true hypoparathyroidism. Biopsies of the parathyroids have been performed in some of the cases, and these revealed normal cytologic structure.

All reported cases have shown a certain characteristic physical appearance with a short stature (Fig. 1), and shortening of the long bones in relation to the trunk. The hands are usually short, stubby and fat with short rounded fingers. According to Albright and associates, the cause of the brachydactylia is early closure of the epiphyses. The face is round and the neck is thick.

Beside the characteristic physical findings, the failure to respond to the intravenous administration of parathyroid hormone provides the final criterion for the diagnosis. This refractoriness of the individual to the hormone has been found in all reported cases. According to Albright and associates (1) the resistance to parathyroid extract can readily be demonstrated by the Ellsworth-Howard test. This test is based on the fact that the first metabolic change following the administration of parathyroid hormone is an increase in phosphate excretion in the urine; the test comprises the intravenous administration of 2 cc. (200 units) of parathyroid extract to the fasting subject, and the determination of the phosphorus content of urine specimens hourly for three hours before medication and for three to five hours after medication.

Normal individuals and true hypoparathyroid individuals respond to this test with an immediate and marked increase in urinary phosphate excretion (Figs. 2 and 3; and Table 1). The serum phosphorus decreases

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and the serum calcium increases. In pseudohypoparathyroid individuals there is no response (Table 1).

The patient here reported showed both the physical characteristics of pseudohypoparathyroidism as well as positive results with the Ellsworth-Howard test. It answers the criteria as outlined by Albright and associates.

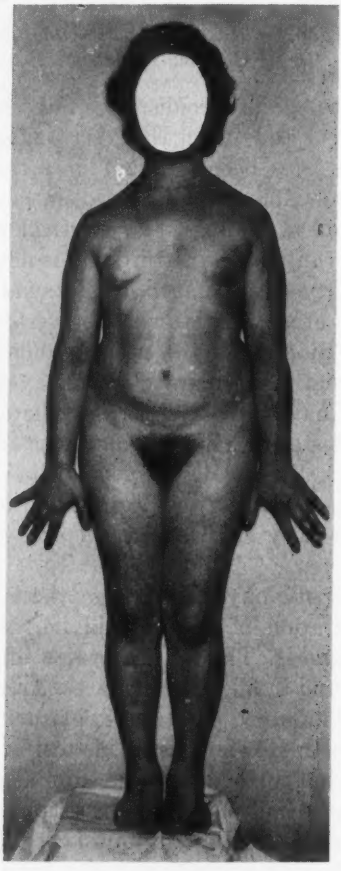

FIG. 1. Short stature in pseudohypoparathyroidism.

There was a good response to dihydrotachysterol. The patient had convulsions, a low serum calcium and a high serum phosphorus. One other feature that may be of importance is the reduced sugar tolerance which was present on two occasions. We have not seen any reports of a similar finding in other cases. Alexander and Tucker's (5) patient had a brother who died of diabetes.

Both parents of our patient were short in stature and the mother had had a thyroidectomy for an adenoma.

The fact that in our case there was a lowered sugar tolerance does not indicate that this is part of the syndrome, but it would be of interest to determine if it is. Future studies of other cases will decide this question.

The inability to respond to parathyroid extract is apparently a singular characteristic of pseudohypoparathyroidism.

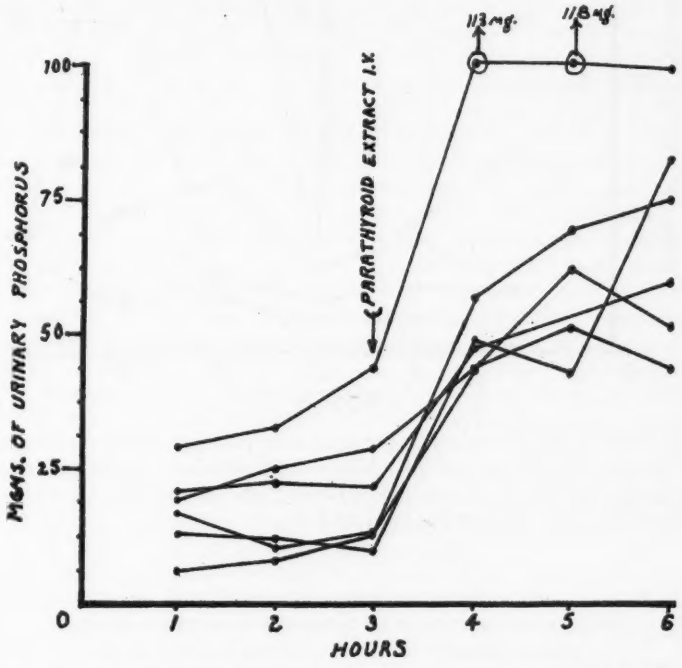

FIG. 2. Showing the type of curve obtained from plotting the urinary phosphorus excretion in normal subjects, before and after intravenous parathyroid extract. (Data *from Ellsworth and Howard* (7).)

CASE HISTORY

A 19-year-old female of Armenian extraction, at the age of 11 (1940) began having "unconscious spells." The onset was spontaneous. These attacks were in the nature of periods of unconsciousness lasting from one to two minutes, and were initiated without an aura. They were accompanied by jerking of the arms and legs. There was no frothing at the mouth, tongue biting or incontinence. The frequency of attacks varied from one to three daily, and depended somewhat on the previous excitement. She had been given capsules "for her nerves," but the seizures were never well controlled.

In March 1944, she was seen by one of us (R.C.M.). At this time the attacks were

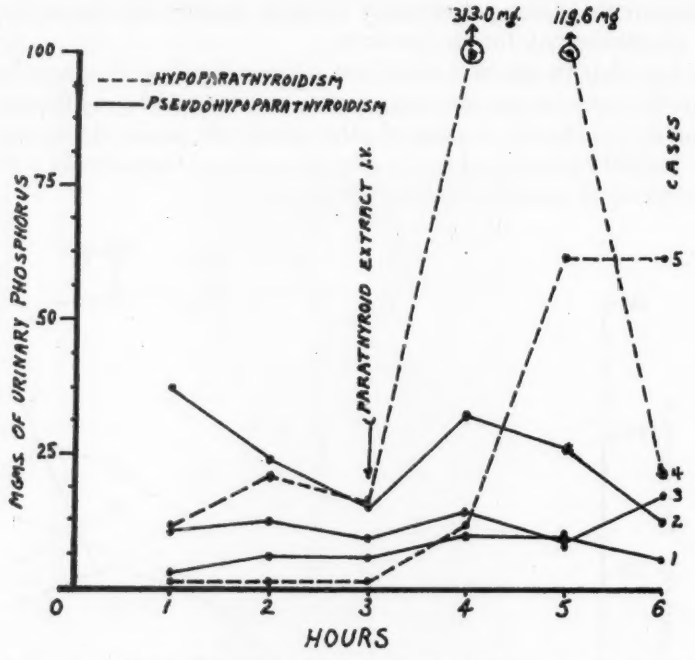

FIG. 3. Showing the type of curve obtained from plotting urinary phosphorus excretion in hypoparathyroidism and pseudohypoparathyroidism, before and after intravenous parathyroid extract. (Cases 1, 3 and 4 are *from Albright et al.* (*1*); Case 5 is *from Ellsworth and Howard* (7); Case 2 is our case.)

TABLE 1. URINARY PHOSPHORUS EXCRETION (MG. PER HOUR) BEFORE AND AFTER THE INTRAVENOUS INJECTION OF PARATHYROID EXTRACT IN HYPOPARATHYROIDISM AND PSEUDOHYPOPARATHYROIDISM

Hours	Hypoparathyroidism	Pseudohypoparathyroidism		
		I*	II*	III
1	11.2	1.53	9.3	37.4
2	20.9	4.14	12.2	23.5
3	15.7	4.01	8.9	14.6
	200 Units parathyroid extract			
4	313.0	9.74	14.7	32.3
5	119.6	9.03	7.9	26.4
6	22.7	4.11	16.3	12.5

* Cases taken *from Albright et al.* (*1*). III is our case.

preceded by dizziness and weakness of the legs, usually beginning in the left leg. System review revealed myopia and clearing of the throat when nervous. Developmental history showed that her birth weight was 8 pounds (3.1 Kg.), she walked at 18 months, and gained weight rapidly. Menstrual history: menarche at 14 years; her periods were of five days' duration and were profuse but regular and painless. Family history: her father was living and well, weighed 145 pounds (65.9 Kg.) and was 63 inches in height (160 cm.); her mother was living and well, weighed 150 pounds (68.1 Kg.) and was 62 inches in height (157.4 cm.).

The physical examination revealed that the patient was a short thick, heavy, round-faced white female with brown hair and eyes. The eyebrows were bushy. Her height was 57½ inches (146 cm.) and weight 121 pounds (55 Kg.) (Fig. 1). The teeth were broad and had enamel defects; pyorrhea was present. The palate was of the high-arched type. The tonsils were absent. A few enlarged, non-tender cervical lymph glands were present; the thyroid gland was palpable. The heart and lungs were normal. The blood pressure was 110 mm. of Hg. systolic and 76 mm. diastolic. The extremities were shorter than normal. Hirsutism of the arms and legs was present. The hands appeared shorter than normal.

Because there was a possibility of a local brain lesion she was referred to a neurosurgeon who diagnosed the condition as epilepsy and prescribed Dilantin.

She was not seen again until February of 1948, at which time the examination was essentially the same, except for the presence of Chvostek and Trousseau signs. Because of these signs the patient was admitted to Harper Hospital on May 16, 1948, for calcium studies. A routine blood count and urinalysis and a urinary Sulkowitch test gave normal results. The serum calcium was 4.7 mg. per cent. A glucose tolerance test[1] was performed which showed a decreased tolerance (Table 2). The blood cholesterol was 344 mg. per cent. The electrocardiogram showed a prolonged RT interval of .34 second. The electroencephalogram was typical of a convulsive disorder, as reported by Dr. A. Derbyshire.

TABLE 2. RESULTS OF GLUCOSE TOLERANCE TESTS PERFORMED ON 5-19-48 AND 8-10-49 RESPECTIVELY
(Urine specimens were all sugar-free.)

Blood sugar (mg. per 100 cc.)						
Fasting	½ hr.	1 hr.	2 hr.	3 hr.	4 hr.	5 hr.
100	197	233	209	122	50.8	64.0
108	235	220	174	124		

She was discharged from the hospital on May 20, 1948, and was given capsules of dihydrotachysterol (0.625 mg. each), two capsules every other day; the dose was then increased to 1.25 mg. daily, and in addition calcium gluconate was given in a dose of 1 Gm. three times a day. The blood calcium increased and the frequency and severity of attacks were markedly decreased. Because her history and stature were so similar to those in the cases of pseudohypoparathyroidism reported by Albright and associates, she was readmitted to Harper Hospital on August 7, 1949, for further study.

The second hospital admission showed the following laboratory findings: serum chloride, 99 mEq. per liter; sodium, 150 mEq. per liter; nonprotein nitrogen, 24 mg. per

cent; total protein, 7.9 Gm. per cent; albumin, 4.05 Gm.; globulin, 3.04 Gm.; A/G ratio, 1/33/1; calcium, 7.4 mg. per cent; and phosphorus, 9.3 mg. per cent. A glucose tolerance test[1] again showed decreased glucose tolerance (Table 2). The Ellsworth-Howard test demonstrated a failure to respond to parathyroid extract (Table 1). On September 9, the serum cholesterol was 285 mg. per cent; and esters, 231 mg. or 81 per cent. The plasma CO_2 combining power was 53 vol. per cent, and serum alkaline phosphatase, 3.0 (Bodansky units). Basal metabolic rates were minus 13 per cent and minus 10 per cent.

The report on the roentgenograms of the teeth was as follows: "The upper right and left third molars are unerupted. The pericoronal spaces about both of these teeth are abnormally wide for the degree of development. There is a supernumerary tooth just distal to the upper left third molar in the process of formation. The lower right and left third molars and the lower right second bicuspid are unerupted. The lower left second bicuspid appears to be incompletely erupted. Caries is also present."

Roentgenograms of the skull, chest, and feet revealed nothing abnormal. The left tibia and fibula showed a slight increase in the density of the trabeculae of the proximal end of the tibia. The study made of the pelvis revealed coarse trabeculations of the ilia; the acetabulums and heads and necks of both femurs also showed these same coarse trabeculations.

It is of interest that Alexander and Tucker's patient had some unerupted teeth which was also true of our case. This may be of clinical significance. The prolonged RT interval seen in the electrocardiograph is a feature of hypocalcemia.

A duoparental inheritance of a short stature was apparently transmitted to the patient.

SUMMARY

A case is reported of pseudohypoparathyroidism in a 19-year-old girl who had convulsions, tetany, a low serum calcium, and a high serum phosphorus.

The syndrome responded to treatment with dihydrotachysterol and calcium.

Unerupted teeth were present; this condition is also reported in at least one other case in the literature.

A lowered glucose tolerance was observed.

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[1] Preparation for the glucose tolerance test was as follows: The patient was given a diet consisting of 300 Gm. of carbohydrate, 80 Gm. of protein, and 120 Gm. of fat,—total calories, 2600 daily for two days. The diet was under the supervision of the Dietetics Department.

Following the three-day preparation, she was given orally 100 Gm. of glucose.

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LETTER TO THE EDITOR

THE ADVANTAGES OF COMBINED ESTROGEN-ANDROGEN THERAPY OF THE MENOPAUSE

To the Editor:

Since the advent of therapy with the gonadal steroid hormones the management of the menopausal syndrome has undergone an interesting transition. In the past fifteen years not only estrogens but also androgens have been successfully applied for the symptomatic relief of menopausal symptoms. The past eight years of satisfactory personal experience with oral estrogen-androgen mixtures was culminated by a two-year clinical study by Glass and Shapiro[1] for the critical evaluation of combined estrogen-androgen therapy in the menopause. This investigation was carried out in over 100 patients who were given four batches of tablets which were similar in appearance but of different composition. These four types of tablet were identified in code[2] and consisted of 1) a placebo, 2) diethylstilbestrol 0.25 mg., 3) methyltestosterone 5 mg., and 4) a tablet, combining both 2) and 3). Careful comparisons made with all of these tablets revealed that over 70 per cent of the patients preferred the mixture. A buccal tablet[3] made up of crystalline estrogen 0.5 mg. and testosterone 2.5 mg. induced similar beneficial effects in a substantial number of these patients, suggesting that tablets when given by the buccal route, even in lower dosage, may suffice for optimum symptomatic relief.

Effective dosage of combined estrogen-androgen tablets was found to be markedly less than that of either hormone given separately. Withdrawal bleeding or andromimetic effects was rarely seen after many weeks of maintenance therapy. The striking superiority of such oral estrogen-androgen preparations may be said to be derived from the following fairly obvious advantages:

1. Inasmuch as women, like men, manifest both androgenic and estrogenic activity, both hormones may be required to provide a more balanced physiologic replacement therapy.
2. The estrogens and androgens are additive in their hormonal suppression of the overactive gonadotropic function of the pituitary.
3. Synergistic effects of the mixture are also seen in their beneficial trophic properties on the vaginal epithelium.

[1] Reported at the meeting of the American Medical Association in San Francisco, June, 1950.

[2] Kindly provided by Dr. D. C. Hines, Lilly Research Laboratories.

[3] Kindly supplied by Mr. Douglas Bailey of Marlyn Company under the trade name of Test-Estrin.

4. The anabolic synergism of the androgen-estrogen combination provides a truly tonic sense of well being, an essential objective in the treatment of the menopausal patient.
5. The testosterone in the mixture permits a sharp reduction in the dosage of estrogen, which tends to cancel out the uterine growth-stimulating and bleeding potential of the estrogen.
6. A smoother transition from a reproductive to a nonreproductive physiology is attained with a minimum of artificial interference with the 'normal' changes incident to the menopause.
7. The androgen-estrogen mixtures elicit better responses in those patients who are refractory to estrogens. Even the psychoneurotic patient responds more favorably, largely because of the greater tonic (anabolic) properties of the androgen-estrogen mixture, which imparts the optimum sense of well being. It is for such reasons that relatively superficial psychotherapy becomes more effective in those patients who require more than hormones for relief.
8. Since testosterone improves the sexual response in women, the use of the androgen-estrogen combination provides some reassurance to the climacteric female that she is not failing in her psychosexual life.
9. The small dose of testosterone in the mixture rarely induces hypertrichosis or other androgenic effects which were not present prior to treatment.
10. The minimal dosage of estrogen used in the combination rarely induces withdrawal bleeding, thus avoiding the need for diagnostic curettage, which is sometimes necessary following large doses of estrogens, in order to rule out the possibility of uterine malignancy. Likewise, benign tumors of the breast or uterus are less apt to be stimulated by the androgen-estrogen mixture, thus avoiding unnecessary surgery. Too many women are needlessly hysterectomized because of benign fibromyomata which usually regress spontaneously at the time of the menopause unless stimulated artificially by large doses of estrogens.

These advantages have prompted the routine application of estrogen-androgen therapy in this clinic for the management of the menopausal syndrome in the past eight years. Inasmuch as the climacteric is of variable duration and symptoms frequently persist for many months or years, it is incumbent upon the clinician to provide the patient with that treatment which is characterized by simplicity, safety and economy. It is possible to meet such specifications by a single tablet combining minimal doses of estrogen and androgen.

S. J. Glass, M.D.

Endocrine Clinic,
Cedars of Lebanon Hospital,
Los Angeles, California.

The Association for the Study of Internal Secretions

THE 1951 ANNUAL MEETING

The Thirty-third Annual Meeting of the Association for the Study of Internal Secretions will be held at the Chalfonte-Haddon Hall Hotel, Atlantic City, New Jersey. The Scientific Sessions have been extended to three days, Thursday, Friday, and Saturday, June 7-8-9.

The Local Chairman of Arrangements is Dr. Matthew Molitch.

Due to the advance in the date of our meeting, Chalfonte-Haddon Hall Hotel will be unable to accommodate all of our members by reason of a previous commitment. The Colton Manor, on Pennsylvania Avenue near Haddon Hall, is an excellent hotel, which has been recently refurnished, and is holding one hundred rooms for our members on the "first come, first served" basis. The Hotel Strand, at Pennsylvania Avenue and the Boardwalk, has also promised to supply a limited number of rooms. It is important that reservations be made immediately if you are to avoid disappointment.

All Scientific Sessions will be held in the Chalfonte-Haddon Hall Hotel. The rooms, in which the session will be held, will be announced in the program and on the hotel bulletin board. The Annual Dinner is scheduled for Friday, June 8, at 7:30 P.M. in the Rutland Room, preceded by cocktails at 6:30 P.M. in the adjoining Benjamin West Room.

Those wishing to present papers, which will be limited to ten minutes, should send four copies of the title and abstract to the Vice-President, Dr. Jane Russell, School of Medicine, Emory University, Atlanta, Georgia, not later than *March 1, 1951. It is imperative that the abstracts be informative and complete with results and conclusions in order that they may be of reference value and suitable for printing in the program and journals of the Association.* The following regulations for the preparation of abstracts and titles must be carefully followed to insure consideration of the paper for the program:

1. Abstracts may not exceed two hundred words, or equivalent space, exclusive of title. No footnotes or acknowledgments to sponsors can be published. References, if used, must be placed in the body of the

text. The abstract should consist of a single paragraph, if possible. Structural chemical formulas cannot be used.

2. The title heading must be arranged as follows:
   Line 1. Title, not to exceed fifteen words.
   Line 2. Author/s. The name of each non-member author collaborating with member-authors is to be followed by the phrase "(by invitation)." Names of non-members who are introduced, *i.e.*, who are not collaborators with member-authors, are to be followed by the phrase "(introduced by . . .)." The principal degree, *e.g.*, M.D., of each author should be given after his name.
   Line 3. Institution of origin and city in which institution is located.
3. The body of the abstract, typed double-space, should follow the heading. The original copy should be on bond paper. There should be three copies.
4. Abstracts should be letter-perfect, since there will be no opportunity for proof reading by authors.

(For details about the type of program, *see* the President's Letter to the Editor on page 1355 of the October 1950 issue.)

THE 1951 AWARDS AND FELLOWSHIPS

Fellowships

THE AYERST McKENNA AND HARRISON FELLOWSHIP

The Ayerst, McKenna and Harrison Fellowship was first awarded in 1947 to Dr. Samuel Dvoskin and in 1948 to Dr. Ernest M. Brown, Jr. Dr. Brown was re-elected for the Fellowship in 1949, and the 1950 Fellowship was awarded to Dr. Lawrence E. Shulman.

THE SCHERING FELLOWSHIP IN ENDOCRINOLOGY

The Schering Fellowship in Endocrinology was established in 1949 and the first recipient was Dr. D. Laurence Wilson, who also received the 1950 Fellowship.

Association Fellowships are designed to assist men or women of exceptional promise in their progress toward a scientific career in endocrinol-

ogy. Fellowships may be awarded to an individual who possesses the Ph.D. or M.D. degree or to a candidate for either of these degrees. The stipend, which will not exceed $2,500.00, may be divided into two Fellowships in varying amounts in accordance with the qualifications of the appointee. The Committee will, in reviewing the proposed program of study, consider the amount of time which the Fellow intends to spend in course work and/or teaching. He must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals. He must submit a program of proposed study, indicate one or more institutions where the proposed program will be followed, and submit statements of approval from the investigators with whom he proposes to conduct his research. He must serve full time if awarded a Fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

Awards

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb & Sons Award of $1,000.00 was established in 1929, and was given first in 1940 to Dr. George W. Corner; in 1941 to Dr. Philip E. Smith; in 1942 to Dr. Fred C. Koch; in 1944 to Dr E. A. Doisy; in 1945 to Dr. E. C. Kendall; in 1946 to Dr. Carl G. Hartman; in 1947 to Drs. Carl F. and Gerty T. Cori; in 1948 to Dr. Fuller Albright; in 1949 to Dr. Herbert M. Evans; and in 1950 to Dr. C. N. H. Long. In 1943 no award was given. A special committee of five members of the Association selects the recipient from among investigators in the United States or Canada, on the basis of outstanding contributions to endocrinology.

THE CIBA AWARD

The Ciba Award to recognize the meritorious accomplishment of an investigator not more than thirty-five years of age in the field of clinical or preclinical endocrinology was established in 1942, but no recipient was selected in 1942 or 1943. In 1944 the award was presented to Dr. E. B. Astwood; in 1945 to Dr. Jane A. Russell; in 1946 to Dr. Martin M. Hoffman; in 1947 to Dr. Choh Hao Li; in 1948 to Dr. Carl Heller; in 1949 to Dr. George Sayers; and in 1950 to Dr. Oscar M. Hechter. The Award is for $1,200.00. If within twenty-four months of the date of the Award, the

recipient should choose to use it toward further study in a laboratory other than that in which he is at present working, it will be increased to $1,800.00.

NOMINATIONS

Each member has the privilege of making one nomination for each Fellowship or Award. A nomination should be accompanied by a statement of the importance of the nominee's contributions to, or interest in, endocrinology and by a bibliography of the nominee's most important publications, with reprints if possible. The nominations should be made on special application forms which may be obtained from the *Secretary, Dr. Henry H. Turner,* 1200 North Walker Street, Oklahoma City 3, Oklahoma, and returned to him *not later than March 15, 1951.*

The American Goiter Association

THE 1951 ANNUAL MEETING

THE 1951 annual meeting of the American Goiter Association will be held in Columbus, Ohio, on May 24, 25, and 26. The Deshler-Wallick Hotel, Broad and High Streets, will be the headquarters and every effort will be made by the hotel officials to make the meeting a success and the visit a very pleasant one. It would be well to see that reservations are made now.

The president, Dr. T. C. Davison, and the chairman of the Local Arrangements Committee, Dr. George Curtis, are planning an excellent meeting. It is hoped that there will be a large attendance of members.

GEORGE C. SHIVERS, M.D.,
Corresponding Secretary,
Colorado Springs, Colo.

VAN METER PRIZE AWARD FOR 1951

THE American Goiter Association again offers the Van Meter Prize Award of three hundred dollars, and two Honorable Mentions for the best essays submitted concerning original work on problems related to the

thyroid gland. The Award will be made at the annual meeting of the Association which will be held in Columbus, Ohio, May 24, 25, 26, 1951, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English; and a typewritten double spaced copy in duplicate sent to the Corresponding Secretary, Dr. George C. Shivers, 100 East Saint Vrain Street, Colorado Springs, Colorado, *not later than March 1, 1951.* The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association.

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International Symposium on Steroids

A SYMPOSIUM on steroids in clinical and experimental practice will be held in Cuernavaca, Mexico, January 15 to 18, 1951 under the auspices of a committee of industrial and institutional scientists.

Membership in the conference is limited by invitation to those individuals nominated either by the committee from the United States or by a Mexican sub-committee. The January conference will deal with the present status of the non-11-oxygenated steroids and an effort will be made to evaluate clinical therapy with such steroids in the fields of rheumatology and cancer.

The work of experimental investigators will be related to clinical findings and it is hoped that, as a result of this meeting certain recommendations will be made as to the course of future clinical and experimental research.

Seeking to evaluate the status of non-11-oxygenated steroids, especially in rheumatology, the committee has noted that only a few compounds of this nature actually have undergone widespread clinical investigation.

One of the compounds in this category is pregnenolene, concerning which divergent opinions and findings have been reported in the medical press. To appraise objectively the work done with pregnenolene, the committee has decided to devote a substantial part of the time allotted for the conference to the study of the most recent work with the compound. At the same time reports will be submitted on investigations with a wide variety of other steroids.

The sessions of the conference will be devoted to a series of 30-minute presentations of papers, followed by extensive discussion. A deliberate effort has been made to invite participants with divergent viewpoints, in the hope that free and informal discussion may eliminate many differences, establish possible points of agreement or delineate paths for future work.

The proceedings of the conference will be recorded and will be published as rapidly after the close of the sessions as possible. Final editing of the proceedings will be in the hands of the arrangements committee and the volume will be issued by one of the leading scientific publishers.

The sponsoring committee comprises Dr. Konrad Dobriner, Sloan-Kettering Institute for Cancer Research, New York; Dr. Paul Holbrook, Tucson, Arizona; Dr. Gregory Pincus, Worcester Foundation for Experimental Biology, Shrewsbury, Mass.; Dr. E. C. Reifenstein, Jr., Research Institute, Oklahoma Medical Research Foundation, Oklahoma City, Okla.; Dr. I. V. Sollins, Chemical Specialties Co., Inc., New York, N. Y. and Syntex S. A., Mexico City, D. F.; and Dr. Abraham White, Univ. of California.

The Mexican sub-committee consists of Dr. Javier Robles Gil, chief of the department of rheumatology of National Institute of Cardiology; Dr. Francisco Gomez Mont, School of Medicine, National University of Mexico; and Dr. Federico A. Lehmann, medical director of Laboratories Hormona, S. A., Mexico City, D. F.

The invited group includes clinical workers in rheumatology, cancer and other diseases, as well as experimental workers in the fields of biology, biochemistry and pharmacology.

In addition to those serving on the sponsoring committee, other participants include: Dr. Samuel H. Bassett, Veterans Administration Center, Los Angeles, Calif.; Dr. Walter Bauer, Harvard School of Medicine, Harvard University, Cambridge, Mass.; Dr. Jerome W. Conn, Division of Metabolism and Endocrinology, University Hospital, Ann Arbor, Mich.; Dr. Roland A. Davison, Stanford University Medical School, San Francisco, Calif.; Dr. Ralph Dorfman, Western Reserve University, Cleveland, Ohio; Dr. William A. Feirer, Norberth, Pa.; Dr. Harry Freeman, Worcester Foundation for Experimental Biology, Shrewsbury, Mass.; Dr. Roy Hertz, National Cancer Institute, Bethesda, Md.; Dr. Freddy Homburger, Tufts College Medical School Cancer Research and Cancer Control Unit, Boston, Mass.; Dr. Thomas H. McGavack, New York Medical College, Metropolitan Hospital Research Unit, Welfare Island, New York, N. Y.; Dr. Louis H. Nahum, Yale University, New Haven, Conn.; Dr. Ira T. Nathanson, Massachusetts General Hospital, Boston, Mass.; Dr. George Sayers, University of Utah, School of Medicine, Salt Lake City, Utah; Dr. Albert Segaloff, Alton Ochsner Medical Foundation, New Orleans, La.; Dr. Richard T. Smith, Philadelphia, Pa.; Dr. Randall G. Sprague, Mayo Clinic, Rochester, Minn.; and Dr. Robert M. Stecher, Western Reserve School of Medicine, Cleveland, Ohio.

BOOKS RECEIVED

THE following list acknowledges receipt of books which it has not been possible for us to review as yet:

American Lectures in Endocrinology. Edited by WILLARD O. THOMPSON, M.D., Clinical Professor of Medicine, University of Illinois College of Medicine, Chicago, Illinois. Charles C Thomas, Publisher, Springfield, Illinois.

The Clinical Use of Testosterone. By HENRY H. TURNER, M.D., Clinical Professor of Medicine, School of Medicine, University of Oklahoma, Oklahoma City, Okla.; 77 pages; 9 figures; 260 references; 1950. Price $2.25.

On the Experimental Morphology of the Adrenal Cortex. By HANS SELYE, M.D., Ph.D., D.Sc., F.R.S.(C), Professor and Director of the Institute of Experimental Medicine and Surgery, University of Montreal, Montreal, Canada, and HELEN STONE, B.Sc., Institute of Experimental Medicine and Surgery, Montreal; 115 pages; 7 tables; 65 illustrations; 1950. Price $2.25.

Types of Diabetes Mellitus and Their Treatment. By ARTHUR R. COLWELL, M.D., Professor of Medicine and Head of the Department, Northwestern University Medical School; Attending Physician, Evanston Hospital; Consulting Physician, Wesley Memorial Hospital, Chicago, Illinois; 103 pages; 18 tables; 6 figures; 1950. Price $2.25.

American Lectures in Medical Physics. Edited by OTTO GLASSER, Ph.D., Department of Biophysics, Cleveland Clinic Foundation, Cleveland, Ohio; Charles C Thomas, Publisher, Springfield, Illinois.

Electrophoresis in Physiology. By LENA A. LEWIS, Ph.D., Research Division, Cleveland Clinic, Cleveland, Ohio; 72 pages; 3 tables; 5 figures, 1950. Price $1.85.

American Lectures in Medicine. Charles C Thomas, Publisher, Springfield, Illinois.

Urgent Diagnosis Without Laboratory Aid. By PROF. DR. HANNS L. BAUER, a.o. Professor of Internal Medicine, University of Munich; formerly Medical Director and Physician-in-Chief, Hospital Munich-Schwabing; 104 pages; 1950. Price $2.00.

American Lectures in Radiation Therapy. Edited by MILTON R. FRIEDMAN, M.D., Associate Professor of Radiology and Associate Radiologist, University Hospital, New York University-Bellevue Medical Center, New York; Charles C Thomas, Publisher, Springfield, Illinois.

The Clinical Use of Radioactive Isotopes. By BERTRAM V. A. LOW-BEER, M.D., Associate Professor of Radiology, University of California Medical School, San Francisco, California; 436 pages; 41 tables; 105 illustrations (some in color); 327 references; 1950. Price $9.50.

Color Atlas of Pathology. Prepared under the auspices of the U. S. Naval Medical School of the National Naval Medical Center, Bethesda, Maryland; 557 pages; illustrated with 1053 figures in color on 365 plates; 1950. J. B. Lippincott Co., Philadelphia, Pa. Price $20.00.

Conference on Cybernetics. Circular Causal, and Feedback Mechanisms in Biological and Social Systems. Transactions of the Sixth Conference, March 24–25, 1949, New York. Edited by HEINZ VON FOERSTER, Department of Electrical Engineering, University of Illinois, Urbana, Illinois; 209 pages; 12 figures; 1950. Josiah Macy, Jr. Foundation, New York, N. Y. Price $3.50.

Cytology of the Human Vagina. By INÉS L. C. DE ALLENDE, M.D., Chief of the Division of Endocrinology, Mercedes and Martin Ferreyra Institute of Medical Investigation; and OSCAR ORÍAS, M.D., Director of the Institute, Córdoba, Argentina.

Foreword by B. A. Houssay, M.D.; translated from the Spanish by G. W. Corner, M.D.; 307 pages; 23 tables; 75 illustrations (some in color); 141 references; 1950. Paul B. Hoeber, Inc., New York, N. Y. Price $7.50.

The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. By Lawson Wilkins, M.D., Associate Professor of Pediatrics, The Johns Hopkins University, The Harriet Lane Home and The Johns Hopkins Hospital, Baltimore, Md.; 405 pages; 32 tables; 150 illustrations; 1061 references; 1950. Charles C Thomas, Publisher, Springfield, Illinois. Price $13.00.

The Merck Manual of Diagnosis and Therapy. A Source of Ready Reference for the Physician. Golden Anniversary eighth edition; 1600 pages; 1950. Merck and Co., Inc., Rahway, N. J. Price $4.50; thumb-index edition, $5.00.

Problems of Infancy and Childhood. Transactions of the Third Conference, March 7–8, 1949, New York. Edited by Milton J. E. Senn, M.D., Departments of Pediatrics and Psychiatry, Yale University School of Medicine, New Haven, Conn.; 156 pages; 1949. Josiah Macy, Jr. Foundation, New York, N. Y. Price $1.25.

Progress in Gynecology. Volume II. Edited by Joe V. Meigs, M.D., Clinical Professor of Gynecology, Harvard Medical School; Chief of Staff of the Vincent Memorial Hospital, the Gynecological Service of the Massachusetts General Hospital; and Somers H. Sturgis, M.D., Clinical Associate in Gynecology, Harvard Medical School; Assistant Surgeon, Massachusetts General Hospital, Boston, Mass.; 836 pages; 23 tables; 186 figures; 1950. Grune & Stratton, Inc., New York, N. Y. Price $9.50.

Renal Function. Transactions of the First Conference, October 20–21, 1949, New York. Edited by Stanley E. Bradley, Department of Medicine, College of Physicians and Surgeons, Columbia University; 172 pages; 4 tables; 41 figures (some in color); 1950. Josiah Macy, Jr. Foundation, New York, N. Y. Price $2.50.

A Syllabus of Laboratory Examinations in Clinical Diagnosis. Critical evaluation of laboratory procedures in the study of the patient. Edited by Thomas Hale Ham, B.S., M.D., Assistant Professor of Medicine, Harvard Medical School; Associate Director, Thorndike Memorial Laboratory; Junior Visiting Physician, Boston City Hospital; 508 pages; 91 tables; 49 figures; numerous references; 1950. Harvard University Press, Cambridge, Mass. Price $5.00.

A Symposium on Steroid Hormones. Edited by Edgar S. Gordon. A collection of the major papers presented at the meeting at the University of Wisconsin, Madison, Wisconsin, in 1949; 409 pages; 43 tables; 119 figures; numerous references; 1950. The University of Wisconsin Press, Madison, Wisconsin. Price $6.50.

Tissue Culture Technique. Second edition. By Gladys Cameron, Department of Biology, Washington Square College, New York University; 203 pages; 54 illustrations; 186 references; 1950. Academic Press, Inc., New York, N. Y. Price $4.20.

Tratado de Endocrinologia Clinica. Volumes I and II. By Mario Schteingart, Docente Libre de Patología Médica de la Facultad de Medicina de Buenos Aires; Ex Jefe del Consultorio de Endocrinologia en el Hospital Nacional de Clínicas (Servicio del Prof. M. R. Castex); Ex Médico de Hospitales de la Maternidad de la Sociedad de Beneficiencia de la Capital (Sección Endocrinologia); foreword by B. Zondek; 1185 pages; 246 illustrations (some in color); extensive references; 1950. Editorial Bibliográfica Argentina, Buenos Aires, Argentina.

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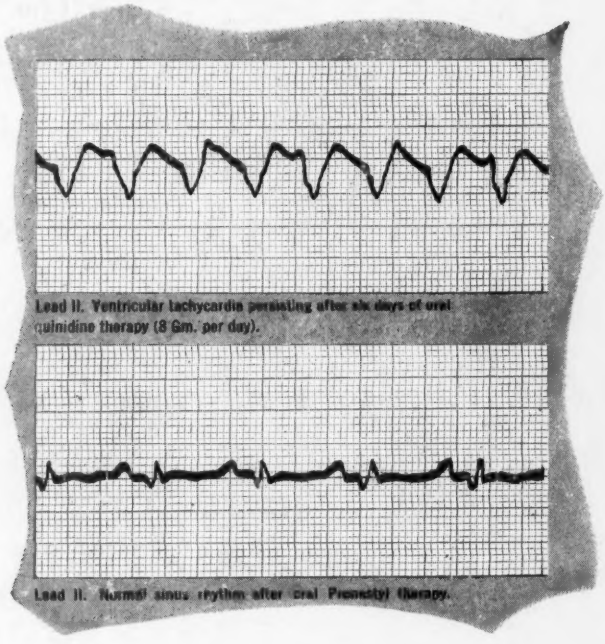

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